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Diabetes e Hipertensão: foco nas metas ou foco nos medicamentos?

SERVIER

DIABETES

Michael Fralick, 2020

D. Giugliano, 2019

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Ashcroft, 2000

Schernthaner, 2003

Aravind, 2012

Rawshani, 2018

Zoungas, 2014

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Lowering of hemoglobin A1C and risk of cardiovascular outcomes and all-cause mortality, a meta-regression analysis☆

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ABSTRACT

Background: The management of type 2 diabetes predominantly focuses on reducing hemoglobin A1C (HbA1c). We examined the association between the magnitude of reduction in HbA1c and cardiovascular outcomes for new diabetes medications: sodium-glucose cotransporter-2 [SGLT2] inhibitors, glucagon-like peptide-1 [GLP1] agonists, and dipeptidyl peptidase-4 [DPP4] inhibitors.
Methods: We reviewed all published, placebo-controlled, randomized cardiovascular outcome trials. Meta-regression was performed to evaluate the association between HbA1c reduction (i.e., [post-intervention HbA1c for active drug – pre-intervention HbA1c for active drug] – [post-intervention HbA1c for placebo – pre-intervention HbA1c for placebo]) and the composite cardiovascular outcome (i.e., stroke, myocardial infarction, or cardiovascular death).
Results: We identified 14 cardiovascular outcome clinical trials, the median sample size was 9401, the median age was 64 years, the median time since diagnosis of diabetes was 12 years, and the median duration of trial follow-up was 120 weeks. Within individual medication classes, each additional 0.5% reduction in HbA1c in the active drug arm, relative to placebo, was associated with a lower incidence of cardiovascular events for GLP1 agonists (0.82, 0.68–0.98) but not for SGLT2 (0.97, 0.69–1.36) or DPP4 (1.03, 0.39–2.74) inhibitors.
Discussion: Our study provides further support that reducing the risk of cardiovascular events for adults with diabetes is partly explained by a reduction in HbA1c.

1. Introduction

Hemoglobin A1C (HbA1c) approximates the average blood sugar value over the preceding three months, and management of patients with type 2 diabetes predominantly focuses on reducing HbA1c.[1–3] While it is commonly used as a surrogate measure for the risk of subsequent cardiovascular events, the evidence that reducing hemoglobin A1C reduces cardiovascular risk is weak.[4,5]

In 2008, the Food and Drug Administration mandated placebo-controlled trials be conducted for new diabetes medications to assess cardiovascular outcomes, rather than HbA1c alone. We examined the association between the magnitude of reduction in HbA1c and cardiovascular outcomes for new diabetes medications: sodium-glucose cotransporter-2 [SGLT2] inhibitors, glucagon-like peptide-1 [GLP1] agonists, and dipeptidyl peptidase-4 [DPP4] inhibitors.

2. Methods

We identified all published, placebo-controlled, randomized cardiovascular outcome trials through the FDA's website. The articles were then identified using MEDLINE. We excluded trials that compared insulin to placebo. The full manuscripts were independently reviewed in duplicate (MF, MC) and disagreements were resolved through consensus. An initial data collection tool was piloted using two studies and revised thereafter based on mutual consensus (MF, MC). We extracted the following data from each article: trial characteristics (e.g., sample size, blinding, duration of follow-up), demographics (e.g., age, sex), comorbid conditions (e.g., hypertension,

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heart failure, stroke), diabetes severity (e.g., baseline hemoglobin A1C, duration of diabetes), and trial outcomes (e.g., change in hemoglobin A1C, risk of primary outcome). Risk of bias was assessed using the Cochrane Risk of Bias Tool.

Meta-regression was performed to evaluate the association between HbA1c reduction (i.e., [post-intervention HbA1c for active drug – pre-intervention HbA1c for active drug] – [post-intervention HbA1c for placebo – pre-intervention HbA1c for placebo]) and the composite cardiovascular outcome (i.e., stroke, myocardial infarction, or cardiovascular death) using random-effects with the DerSimonian-Laird estimator for between-study variability.[6,7] Meta-regression with fixed-effects was also performed restricted to each drug class. All statistical analyses were performed independently by two study members (MF, AO) using R version 3.4.2 or Stata. This study did not require research ethics board approval since it utilized data reported in previously published trials.

3. Results

We identified 14 cardiovascular outcome clinical trials (Fig. 1). All trials were randomized, double-blind, and most trials had a primary cardiovascular composite outcome of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death (N = 12, 86%). Change in HbA1c was reported in the majority of studies as the mean difference between HbA1c in the treatment arm compared to the placebo arm, averaged over the duration of the study (N = 10, 71%).

The median sample size was 9401 (Interquartile range [IQR]: 6296, 13,539), the median age was 64 years (IQR: 63.1, 65.3), the median

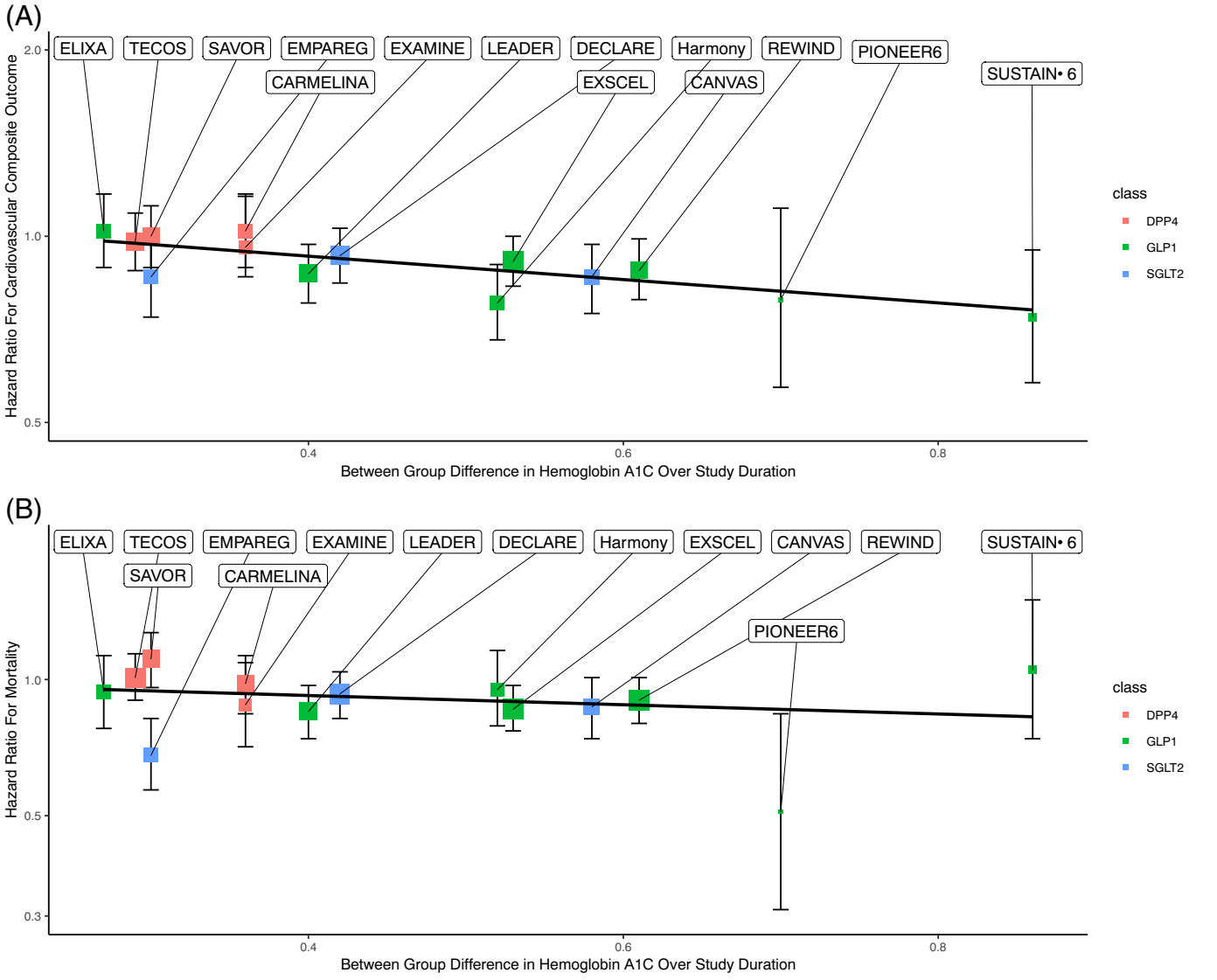

Fig. 1. Association of reduction in hemoglobin A1C, relative to placebo, and the hazard ratio for primary composite cardiovascular outcome (top panel) and all-cause mortality (bottom panel). Legend: Data points (i.e., boxes) were weighted based on the inverse of the variance of the trial's outcome (i.e., hazard ratio for cardiovascular composite outcome for A and hazard ratio for mortality for B). The lines perpendicular to the boxes represent the 95% confidence intervals of the hazard ratio. The overall regression line represents weighted linear regression and grey shading indicates 95% confidence interval. Outcomes, and Mortality in Type 2 Diabetes (EMPAREG); Dapagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (DECLARE-TIMI 58), Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk (CARMELINA); Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes (EXAMINE); Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes (TECOS); Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus (SAVOR-TIMI 53); Albiglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Cardiovascular Disease: a Double-Blind, Randomised Placebo-Controlled Trial (Harmony); Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome (ELIXA); Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes (LEADER); Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6); Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes (EXSCEL), Dulaglutide and cardiovascular outcomes in type 2 diabetes: a double-blind, randomised placebo-controlled trial (REWIND), Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (PIONEER6).

time since diagnosis of diabetes was 12.0 years [IQR: 10.3, 14.1], the median duration of trial follow-up was 120 weeks (IQR: 109, 165). The active treatment arm was GLP1 agonists in 7 trials, SGLT2 inhibitors in 3 trials and DPP4 inhibitors in 4 trials. The median baseline HbA1c was 8.1% (IQR: 7.9, 8.3), the mean body mass index was 31.4 kg/m^2 (standard deviation [SD] = 1.2), 35% of patients were women, 87% had hypertension, and 17% had heart failure. All trials were at low risk of bias.

As anticipated, patients randomized to active treatment had a greater reduction in their HbA1c (range: −0.27% to −0.86%) by the end of the trial compared to patients randomized to placebo (Fig. 1). After controlling for baseline HbA1c, each additional 0.5% reduction in HbA1c in the intervention arm, relative to placebo, was associated with a hazard ratio [HR] of 0.83 (95% Confidence Interval [CI], 0.72–0.94) for the primary composite outcome of cardiovascular events and a hazard ratio of 0.92 (0.73–1.17) for all-cause mortality. Within individual medication classes, each additional 0.5% reduction in HbA1c in the active drug arm, relative to placebo, was associated with a lower incidence rate of cardiovascular events for GLP1 agonists (HR = 0.82, 95% CI 0.68–0.98) but not for SGLT2 inhibitors (HR = 0.97, 95% CI 0.69–1.36) or DPP4 inhibitors (HR = 1.03, 95% CI 0.39–2.74).

4. Discussion

Our study of 14 cardiovascular outcome trials including over 130,000 adults with type 2 diabetes mellitus, identified that reductions in HbA1c were associated with the observed reduction in cardiovascular risk, and this was primarily driven by the trials for GLP1 agonists. This was not the case for SGLT2 inhibitors. For example, dapagliflozin achieved a larger reduction in HbA1c than empagliflozin, but only empagliflozin lowered both cardiovascular outcomes and all-cause mortality.[8] These findings suggest that the improved cardiovascular outcomes may be partially explained by the reduction in HbA1c for GLP1 agonists, but not for SGLT2 inhibitors. Our findings are supported by a recent meta-analysis reporting a similar effect of reduction in hemoglobin A1c on cardiovascular outcomes.[9]

Important limitations of our study include: a small number of available clinical trials for both DPP4 inhibitors and SGLT2 inhibitors (as evidenced by the wide confidence intervals), an inability to account for the type of usual care the placebo group received, varying baseline cardiovascular risk across trials, and ecological bias since we did not have access to individual patient level data.

Our study provides further support that reducing the risk of cardiovascular events for adults with diabetes is only partly associated with changes in HbA1c. In particular, the magnitude of HbA1c reduction may be more relevant for some classes of medications (GLP1 agonists) compared to others (SGLT2 inhibitors). Finally, a modest reduction in HbA1C with an SGLT2 inhibitor does not negate the possibility that a patient can benefit from this class of medications.

Author statement

1. Conceptualization: MF, MC, RG.
2. Data curation: MF, MC.
3. Formal analysis: MF, AO.
4. Funding acquisition: N/A.
5. Investigation: All authors.
6. Methodology: All authors.
7. Project administration: All authors.
8. Resources; Software; Supervision; Validation; Visualization: All authors.
9. Roles/Writing - original draft: MF and MC.
10. Writing - review & editing: All authors.

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RAPID COMMUNICATION

Cardiovascular outcome trials and major cardiovascular events: does glucose matter? A systematic review with meta-analysis

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Abstract

Purpose We did a meta-analysis with meta-regression to evaluate the relationship between hemoglobin A1c (A1C) reduction and the primary CV outcome of cardiovascular outcome trials (CVOTs).

Methods We used a random effects meta-analysis of the 12 CVOTs to quantify the effect of A1C reduction on major cardiovascular events (MACE) risk by stratifying the difference in achieved A1C (drug vs placebo) in three strata: A1c < 0.3%, A1c ≥ 0.3% and < 0.5%, and A1c ≥ 0.5%.

Results We found a relation between the reduction in achieved A1C and the hazard ratio reduction for MACE (P = 0.002), explaining almost all (94.1%) the between-study variances: lowering A1C by 0.5% conferred a significant HRR of 20% (95% CI 4–33%) for MACE.

Conclusions Blood glucose reduction may play a more important role than previously thought in reducing the risk of MACE during treatment with the newer glucose-lowering drugs, including peptidase-4 inhibitors, glucagon-like peptide 1 receptor agonists and sodium–glucose co-transporter-2 inhibitors.

Keywords CVOTs (cardiovascular outcome trials) · Type 2 diabetes · Major cardiovascular events · Glycemic control

Introduction

Tight glycemic control has an imperfect role to reduce the cardiovascular (CV) complications of type 2 diabetes (T2D). Intensive glycemic control with conventional antihyperglycemic drugs can reduce the risk of MACE (major cardiovascular events) by 9% in patients with T2D, leaving a 91% residual vascular risk still remaining [1]. As far as macrovascular complications of T2D are concerned, residual vascular risk may be defined as the risk of MACE that remains after intensive and successful glycemic control [2].

Newer drugs, including dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and sodium–glucose co-transporter-2 inhibitors (SGLT-2 inhibitors), may have a better performance on MACE [2], but this depends on the drug. Cardiovascular outcome trials (CVOTs) of newer glucose-lowering medications have represented a unique opportunity to evaluate their CV effects. However, CVOTs can also be used to assess the role of glycemic control on CV outcomes. We did a meta-analysis with meta-regression to evaluate the relationship between hemoglobin A1c (A1C) reduction and the primary CV outcome of CVOTs.

Methods

We conducted this systematic review and meta-analysis based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines [3]. The PRISMA

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checklist is provided in the Supplementary Data. Databases for search included PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and ClinicalTrials.gov. (http://www.clinicaltrials.gov). The last search was performed on 15 January 2019. The search terms used were "type 2 diabetes", "glycemic control"; "dipeptidyl-peptidase inhibitor", "saxagliptin", "alogliptin", "dapagliflozin", linagliptin"; "glucagon-like peptide-1 receptor agonist", "exenatide", "lixisenatide", "liraglutide", "semaglutide", "dulaglutide", "albiglutide"; sodium-glucose co-transporter-2 inhibitor", "empagliflozin", "canagliflozin", "dapagliflozin"; "major cardiovascular events", and "MACE". The search was filtered to include only randomized controlled trials (RCTs) involving humans. Reference lists of prior reviews and meta-analyses were also manually searched to capture relevant studies that were not indexed by normal keywords.

We included CVOTs if they were RCTs performed in adults with T2D, compared add-on therapy with any DPP-4i, GLP-1 RA or SGLT-2i with placebo, had MACE as primary CV outcome, and reported data of the other MACE components (nonfatal myocardial infarction, nonfatal stroke and CV mortality) required by regulatory agencies for CV safety studies in T2D. We excluded trials if they were completed before the FDA guidance of 2008.

Two investigators (D.G., M.I.M.) used a standardized tool to independently abstract all data, and disagreements were resolved by consensus. After the initial screening of titles and abstracts, the studies included by both reviewers were compared, and disagreement was resolved by consensus. We evaluated the risk of bias of the included RCTs according to the Cochrane Collaboration's tool for assessing the risk of bias [4].

Hazard ratios (HR) and 95% confidence intervals (95% CI) were collected for MACE outcome. Heterogeneity between studies was assessed using the Q statistic and I^2, which is the proportion of total variance observed between the trials attributed to the differences between trials rather than to sampling error. $I^2 < 25\%$ was considered as low in heterogeneity, $I^2 > 75\%$ as high in heterogeneity, and a Q statistic P value of < 0.10 was considered significant. We calculated the summary estimates for CV efficacy outcomes using a random effects model meta-analysis. We quantified the effect of A1C reduction on MACE risk by stratifying the difference in achieved A1C (drug vs placebo) in three strata: A1c $< 0.3\%$, A1c $\geq 0.3\%$ and $< 0.5\%$, and A1c $\geq 0.5\%$. To explore the relationship between the differences in achieved A1C and HRR (hazard ratio reduction), we performed meta-regression analyses. Meta-regression model estimates the amount of heterogeneity related to study characteristics; this model relates the treatment effect to study-level covariates, while assuming additivity of within-study and between-study components of variance. Restricted maximum likelihood estimators were used to estimate model parameters. Permutation test (using 1000 re-allocations) was used for assessing the true statistical significance of an observed meta-regression finding [5, 6]. Data were analyzed using Stata 11.2 software (StataCorp LP, College Station, TX).

Results

Sixty articles were screened for eligibility, and 12 trials were eligible and included in the meta-analysis. All the 12 CVOTs [7–18] were multinational and sponsored by industry (Table 1). The baseline A1C level ranged from 7.3 to 8.7%, without any significant difference between groups (drug vs placebo). The CVOTs evaluated 120,765 patients and the following classes of medications: DPP-4i in 43,522 participants; GLP-1 RAs in 42,920 participants; and SGLT-2i in

Table 1 Main characteristics of the 12 CVOTs included in the meta-analysis

Trial and sample size	Intervention	Follow-up (years)	Primary outcome	HR (95% CI)
SAVOR-TIMI 53 ($n = 16{,}492$)	Saxagliptin/placebo	2.1	3-point MACE	1.0 (0.91, 1.10)
EXAMINE ($n = 5380$)	Alogliptin/placebo	1.5	3-point MACE	0.96 (0.79, 1.16)
TECOS ($n = 14{,}671$)	Sitagliptin/placebo	2.8	4-point MACE	0.98 (0.89, 1.08)
CARMELINA ($n = 6979$)	Linagliptin/placebo	2.2	3-point MACE	1.02 (0.89, 1.17)
ELIXA ($n = 6068$)	Lixisenatide/placebo	2.1	4-point MACE	1.02 (0.89, 1.17)
LEADER ($n = 9340$)	Liraglutide/placebo	3.8	3-point MACE	0.87 (0.78, 0.97)
SUSTAIN-6 ($n = 3297$)	Semaglutide/placebo	3.1	3-point MACE	0.74 (0.58, 0.95)
EXSCEL ($n = 14{,}752$)	Exenatide OW/placebo	3.2	3-point MACE	0.91 (0.83, 1.00)
HARMONY ($n = 9463$)	Albiglutide/placebo	1.6	3-point MACE	0.78 (0.68, 0.90)
EMPA-REG OUTCOME ($n = 7021$)	Empagliflozin/placebo	3.1	3-point MACE	0.86 (0.74, 0.99)
CANVAS ($n = 10{,}142$)	Canagliflozin/placebo	2.4	3-point MACE	0.86 (0.76, 0.98)
DECLARE ($n = 17{,}160$)	Dapagliflozin/placebo	4.2	3-point MACE	0.93 (0.84, 1.03)

34,323 participants. According to the Cochrane Collaboration's tool for assessing risk of bias, there was no major risk of bias in any study (Table 2).

In the overall analysis, the risk of MACE was significantly reduced by 8% with the use of DPP-4i, GLP-1 RAs and SGLT-2i, as compared with placebo, with a significant degree of heterogeneity between trials. Compared with placebo, DPP-4i showed a neutral effect on MACE, while the use of both GLP-1 RAs and SGLT-2i was associated with significant reductions of MACE (12% and 11%, respectively), with significant heterogeneity for GLP-1 RAs and no heterogeneity for SGLT-2i (Table 3).

Figure 1 shows the effect of A1C-lowering (by strata) on MACE risk: there was a linear increment of HRR across A1C strata, with no reduction of risk in CVOTs with a < 0.3% difference in achieved A1C (0%, 95% CI − 0.6–0.6%, $P = 0.895$) to the greater HRR in CVOTs with a ≥ 0.5% difference in achieved A1C (− 13%, − 20 to − 5%, $P = 0.002$). Heterogeneity was not significant in every stratum: A1C < 0.3%, $I^2 = 0\%$, $P = 0.891$; A1C ≥ 0.3% and < 0.5%, $I^2 = 43\%$, $P = 0.117$; and A1C ≥ 5%, $I^2 = 21\%$, $P = 0.285$. There was a relation between the reduction in achieved A1C and the HRR for MACE ($P = 0.002$), explaining almost all (94.1%) of between-study variance: lowering A1C by 0.5% conferred a significant HRR of 20% (95% CI 4–33%) for MACE. There was no relation between the reduction in achieved A1C and the HRR for nonfatal MI ($P = 0.834$) or CV mortality ($P = 0.926$), but there was a significant ($P = 0.002$) relation with nonfatal stroke, with no heterogeneity ($I^2 = 8.6\%$, $P = 0.361$), explaining all the between-study variance (100%).

Discussion

In the pooled analysis of the 12 CVOTs, we found a significant 8% reduction of MACE risk in T2D patients treated with the newer antihyperglycemic drugs, with moderate heterogeneity and no evidence of publication bias. However, only the use of both GLP-1 RAs and SGLT-2i was associated with significant reductions of MACE (12% and 11%, respectively), while the use of DPP-4i was associated with a neutral effect on MACE.

We have also shown a linear relation between the extent of achieved A1C reduction and the risk of MACE, with the larger risk reduction associated with the greater A1C

Table 2 Summary of risk of bias assessment

Trial ID	Random sequence generation[a]	Allocation concealment[a]	Blinding of participants and personnel[b]	Blinding of outcome assessment[b]	Incomplete outcome data[b]	Selective reporting[b]
SAVOR-TIMI 53, 2013	L	L	L	L	L	L
EXAMINE, 2013	L	L	L	L	L	L
TECOS, 2015	L	L	L	L	L	L
CARMELINA, 2019	L	L	L	L	L	L
ELIXA, 2015	L	L	L	L	L	L
LEADER, 2016	L	L	L	L	L	L
SUSTAIN-6, 2016	L	L	L	L	L	L
EXSCEL, 2017	L	L	L	L	L	L
HARMONY, 2018	L	L	L	L	L	L
EMPA-REG, 2015	L	L	L	L	L	L
CANVAS, 2017	L	L	L	L	L	L
DECLARE, 2019	L	L	L	L	L	L

L low risk of bias, *U* unclear risk of bias, *H* high risk of bias

[a]Risk of bias assessment for random sequence generation and allocation concealment is performed at the study level

[b]Risk of bias assessment for blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting are for the primary outcome

Table 3 Overall and subgroup meta-analyses

MACE	Trials (*n*)	Estimate (HR)	95% CI	*P* value	I^2 (%)	*P* value *Q* test
All	12	0.92	0.87–0.96	0.001	45.8	0.041
DPP-4i	4	0.99	0.94–1.05	0.798	0	0.948
GLP-1 RAs	5	0.88	0.80–0.96	0.005	58.8	0.045
SGLT-2i	3	0.89	0.83–0.96	0.001	0	0.550

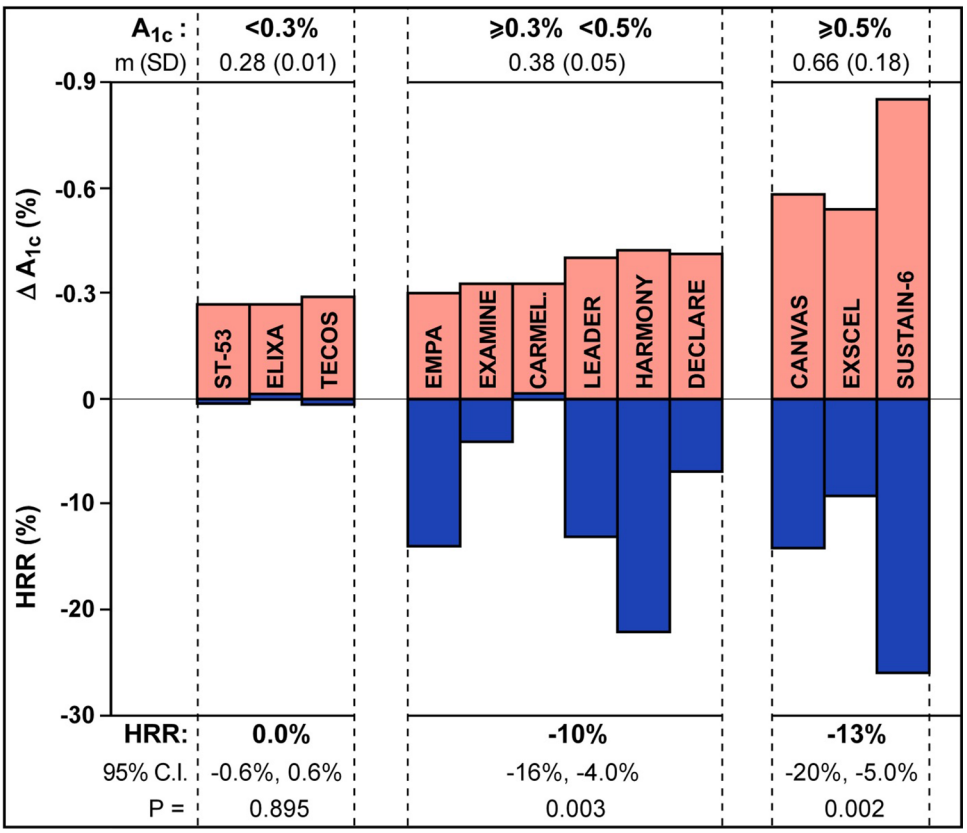

Fig. 1 Effects of CVOTs on the risk of MACE. Top: the reduction, compared to placebo, of A1C in the 12 CVOTs has been divided into 3 strata (A1C < 0.3%, A1C ≥ 0.3% and < 0.5%, A1C ≥ 0.5%) as indicated in orange. Bottom: the corresponding effect on MACE is indicated in blue. *HRR* hazard ratio reduction, *m (SD)* mean and standard deviation, *CI* confidence intervals, *S-53* SAVOR-TIMI 53, *EMPA* EMPA-REG OUTCOME, *CARMEL* CARMELINA

reduction between the treatment and placebo groups. The risk reduction of MACE was almost totally driven by the risk reduction of nonfatal stroke.

All the CVOTs were designed to promote "glycemic equipoise" to minimize the confounding effect of differences in glycemic control. Ironically, those CVOTs that obtained the best equipoise have shown a null effect on MACE. Accordingly, the blood glucose reduction may play a more important role than previously thought in reducing the risk of MACE during treatment with the newer glucose-lowering drugs. Reduced risk of hypoglycemia associated with these drugs may also have played a role, as severe hypoglycemic episodes within the previous 3 months were associated with increased risk for MACE in the VADT trial [19].

In conclusion, we have shown that improved glycemic control by the newer antihyperglycemic drugs (GLP-1 RA and SGLT-2i) may have a more important role in the mediation of their CV benefits than previously thought. Meta-regression is a method to reduce heterogeneity [20], i.e., the variation among studies; even if heterogeneity was not significant in A1C strata, our results are to be considered as exploratory, and should be interpreted always in conjunction with the effect from the subset of studies most relevant to the patients.

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Compliance with ethical standards

Conflict of interest D.G. received honoraria for speaking at meetings from Novartis, Sanofi-Aventis, Lilly, AstraZeneca, and NovoNordisk. M.I.M. received honoraria for speaking at meetings from Lilly and NovoNordisk. K.E. received honoraria for speaking at meetings from Novartis, Sanofi-Aventis, Lilly, AstraZeneca, Boehringer Ingelheim, and NovoNordisk. P.C. declares that he has no conflict of interest. G.B. declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Informed consent For this type of study, informed consent is not required.

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Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study

Irene M Stratton, Amanda I Adler, H Andrew W Neil, David R Matthews, Susan E Manley, Carole A Cull, David Hadden, Robert C Turner, Rury R Holman on behalf of the UK Prospective Diabetes Study Group

Abstract

Objective To determine the relation between exposure to glycaemia over time and the risk of macrovascular or microvascular complications in patients with type 2 diabetes.
Design Prospective observational study.
Setting 23 hospital based clinics in England, Scotland, and Northern Ireland.
Participants 4585 white, Asian Indian, and Afro-Caribbean UKPDS patients, whether randomised or not to treatment, were included in analyses of incidence; of these, 3642 were included in analyses of relative risk.
Outcome measures Primary predefined aggregate clinical outcomes: any end point or deaths related to diabetes and all cause mortality. Secondary aggregate outcomes: myocardial infarction, stroke, amputation (including death from peripheral vascular disease), and microvascular disease (predominantly retinal photocoagulation). Single end points: non-fatal heart failure and cataract extraction. Risk reduction associated with a 1% reduction in updated mean HbA_{1c} adjusted for possible confounders at diagnosis of diabetes.
Results The incidence of clinical complications was significantly associated with glycaemia. Each 1% reduction in updated mean HbA_{1c} was associated with reductions in risk of 21% for any end point related to diabetes (95% confidence interval 17% to 24%, $P<0.0001$), 21% for deaths related to diabetes (15% to 27%, $P<0.0001$), 14% for myocardial infarction (8% to 21%, $P<0.0001$), and 37% for microvascular complications (33% to 41%, $P<0.0001$). No threshold of risk was observed for any end point.
Conclusions In patients with type 2 diabetes the risk of diabetic complications was strongly associated with previous hyperglycaemia. Any reduction in HbA_{1c} is likely to reduce the risk of complications, with the lowest risk being in those with HbA_{1c} values in the normal range (<6.0%).

Introduction

The UK prospective diabetes study (UKPDS), a clinical trial of a policy of intensive control of blood glucose after diagnosis of type 2 diabetes, which achieved a median haemoglobin A_{1c} (HbA_{1c}) of 7.0% compared with 7.9% in those allocated to conventional treatment over a median 10.0 years of follow up, has shown a substantial reduction in the risk of microvascular complications, with a reduction in the risk of myocardial infarction of borderline significance.[1] Complementary information for estimates of the risk of complications at different levels of glycaemia can be obtained from observational analyses of data during the study.

In patients with type 2 diabetes previous prospective studies have shown an association between the degree of hyperglycaemia and increased risk of microvascular complications,[2 3] sensory neuropathy,[3 4] myocardial infarction,[2 5 6] stroke,[7] macrovascular mortality,[8–10] and all cause mortality.[9 11–14] Generally, these studies measured glycaemia as being high or low or assessed glycaemia on a single occasion, whereas repeated measurements of glycaemia over several years would be more informative.

The existence of thresholds of glycaemia—that is, concentrations above which the risk of complications markedly increases—has not been studied often in patients with type 2 diabetes. The relative risk for myocardial infarction seems to increase with any increase in glycaemia above the normal range,[15 16] whereas the risk for microvascular disease is thought to occur only with more extreme concentrations of glycaemia.[17–19] The diabetes control and complications trial (DCCT) research group showed an association between glycaemia and the progression of microvascular complications in patients with type 1 diabetes for haemoglobin A_{1c} over the range of 6-11% after a mean of six years of follow up.[20] No specific thresholds of glycaemia were identified above which patients were at greater risk of progression of retinopathy, increased urinary albumin excretion, or nephropathy.[19–21] Nor has any threshold of fasting plasma glucose concentration been identified for cardiovascular deaths.[22 23]

We evaluated the relation between exposure to glycaemia over time and the development of macrovascular and microvascular complications and compared this with the results of the UKPDS trial of a policy of intensive control of blood glucose control.[1]

Editorial by Tuomilehto

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Details of participating centres, staff, and committees and additional funding agencies are on the BMJ's website.

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Professor Turner died unexpectedly after completing work on this paper

Methods

Participants recruited to the UKPDS

Details are presented in the companion paper (UKPDS 36) published in this issue (see page 412).

Participants in observational analysis

Of 5102 patients, 4585 white, Asian Indian, and Afro-Caribbean patients who had haemoglobin A_{1c} (HbA_{1c}) measured three months after the diagnosis of diabetes were included in analyses of incidence rates. Of these, 3642 with complete data for potential confounders were included in analyses of relative risk. Complete data were required for all participants included in the multivariate observational analyses. For this reason there are fewer (3642) participants in these analyses than in the clinical trial, despite the inclusion of patients not randomised in the trial. Their characteristics are presented in table 1.

Participants in UKPDS blood glucose control study

After a three month dietary run-in period patients were stratified on the basis of fasting plasma glucose concentration and body weight. The 3867 patients who had fasting plasma glucose concentrations between 6.1 and 15.0 mmol/l and no symptoms of hyperglycaemia were randomised to a policy of conventional glucose control, primarily with diet, or to an intensive policy with sulphonylurea or insulin.[1 24–26] The aim in the group allocated to conventional control (n = 1138) was to obtain fasting plasma glucose concentration < 15 mmol/l, but if concentrations rose to ≥15 mmol/l or symptoms of hyperglycaemia developed patients were secondarily randomised to non-intensive use of these pharmacological treatments, with the aim of achieving fasting plasma glucose concentrations < 15 mmol/l without symptoms. The aim in the group allocated to intensive control (n = 2729) was to achieve fasting plasma glucose concentration < 6 mmol/l, primarily with a single pharmacological treatment. Details of treatments and their effect on glucose control have been published elsewhere.[1]

Biochemical methods

Biochemical methods have been reported previously.[27] Haemoglobin A_{1c} was measured by high performance liquid chromatography (Biorad Diamat automated glycosylated haemoglobin analyser), the range for people without diabetes being 4.5% to 6.2%.[27 28] Baseline variables are quoted for measurements after the initial dietary run-in period.

Table 1 Characteristics of patients included in proportional hazards model measured after three month dietary run-in after diagnosis of diabetes and those included in UKPDS glucose control study.[1] Figures are means (SD) unless stated otherwise

	Proportional hazards model of observational data (n=3642)	Clinical trial of intensive *v* conventional blood glucose control policy (n=3867)
Age (years)	53 (8)	53 (9)
Proportion of men (%)	60	61
Ethnicity (% white/Asian Indian/Afro-Caribbean/other)	82/10/8/0	81/10/8/1
Body mass index (kg/m^2)	27.7 (5.3)	27.5 (5.2)
Fasting plasma glucose (mmol/l)*	7.9 (6.6-10)	8.0 (7.1-9.7)
Haemoglobin A_{1c} (%)	7.1 (1.8)	7.1 (1.5)
Systolic blood pressure (mm Hg)	135 (19)	135 (20)
Low density lipoprotein cholesterol (mmol/l)	3.5 (1.0)	3.5 (1.0)
High density lipoprotein cholesterol (mmol/l)	1.06 (0.24)	1.07 (0.24)
Triglyceride (mmol/l)†	1.5 (0.9-2.5)	1.5 (0.9-2.5)
Albuminuria (%)‡	13.3	11.4

*Median (interquartile range).
†Geometric mean (1 SD range).
‡>50 mg/l in single morning sample.

Glycaemic exposure

Exposure to glycaemia was measured firstly at baseline as haemoglobin A_{1c} concentration and secondly over time as an updated mean of annual measurements of haemoglobin A_{1c} concentration, calculated for each individual from baseline to each year of follow up. For example, at one year the updated mean is the average of the baseline and one year values and at three years is the average of baseline, one year, two year, and three year values.

Clinical complications

The clinical end points and their definitions are shown in the box in the companion paper (UKPDS 36) published in this issue (see page 412).

Statistical analysis

Incidence rates by category of glycaemia

The unadjusted incidence rates were calculated by dividing the number of people with a given complication by the person years of follow up for the given complication within each category of updated mean haemoglobin A_{1c} concentration and reported as events per 1000 years of follow up.[29] The categories were defined (median values in parentheses) as: < 6% (5.6%), 6- < 7% (6.5%), 7- < 8% (7.5%), 8- < 9% (8.4%), 9- < 10% (9.4%), and ≥ 10% (10.6%) over the range of updated mean haemoglobin A_{1c} of 4.6-11.2% (1st-99th centile). Follow up time was calculated from the end of the initial period of dietary treatment to the first occurrence of that complication or loss to follow up, death from another cause, or to the end of the study on 30 September 1997 for those who did not have that complication. Hence, follow up time is equivalent to duration of diabetes. For myocardial infarction and stroke for participants who had a non-fatal followed by a fatal event, the time to the first event was used. The rates were therefore for single and not recurrent events. The median follow up time for all cause mortality was 10.4 years.

We calculated adjusted incidence rates for each category of updated mean haemoglobin A_{1c} using a Poisson regression model adjusted for male sex, white ethnic group, age at diagnosis 50-54 years, and duration of diabetes 7.5-12.5 years and expressed in events per 1000 person years of follow up. These parameters were chosen to reflect the median age and duration of diabetes and the modal ethnic group and sex.

Hazard ratio and risk reduction

To assess potential associations between updated mean haemoglobin A_{1c} and complications we used proportional hazards regression (Cox) models. Potential confounding risk factors included in all Cox models were sex, age, ethnic group, smoking (current/ever/never) at time of diagnosis of diabetes, and baseline high and low density lipoprotein cholesterol, triglyceride, presence of albuminuria (> 50 mg/l measured in a single morning urine sample) measured after three months'

dietary treatment, and systolic blood pressure represented by the mean of measures at two and nine months after diagnosis. The hazard ratio was used to estimate the relative risk. At each event time, the updated mean haemoglobin A_{1c} value for individuals with an event was compared with the updated value of those who had not had an event by that time. The updated mean value was included as a time dependent covariate to evaluate glucose exposure during follow up.[20 29 30] It was included as a categorical variable in the categories of glycaemia listed above, with the lowest category (<6%) as the reference category assigned a hazard ratio of 1.0 and with the highest category ≥9%. (This is reflected in the point estimates as shown in figures 3 and 4.) Separate models, with updated mean haemoglobin A_{1c} as a continuous variable, were used to determine reduction in risk associated with a 1% reduction in haemoglobin A_{1c} (see regression lines in figures 3 and 4). We evaluated the presence of thresholds by visual inspection. The 95% confidence intervals were calculated on the basis of the floating absolute risk.[31] Log linear relations are reported by convention.[1 32] The risk reduction associated with a reduction of 1% updated mean haemoglobin A_{1c} was calculated as 100% minus the reciprocal of the hazard ratio expressed as a percentage. The risk reduction from the continuous variable model associated with a 1% reduction in observed haemoglobin A_{1c} was compared with the risk reduction seen in the UKPDS intervention trial of an intensive versus a conventional policy of blood glucose control, for which no adjustment for potential confounders was required as they were balanced by randomisation.[1]

To assess whether the association between mean updated haemoglobin A_{1c} and complications was independent of randomisation, separate models included mean updated haemoglobin A_{1c} and randomisation to either intensive or conventional policy, as well as all potential confounders listed above. The model for all end points related to diabetes included 3005 individuals.

Statistical analyses were performed with SAS version 6.12.[33]

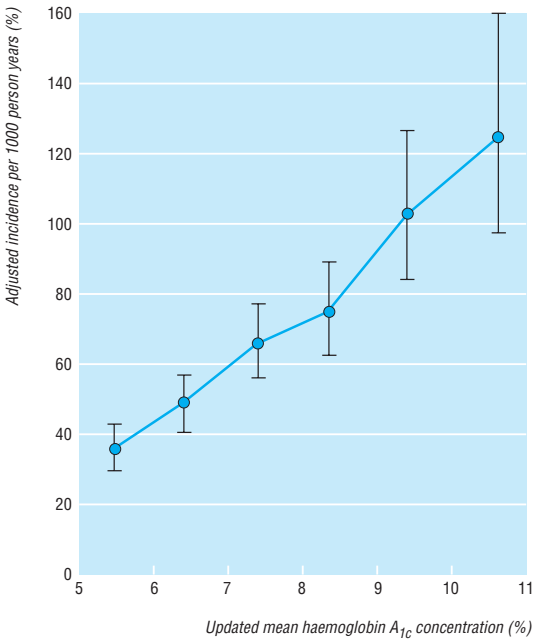

Fig 1 Incidence rate and 95% confidence intervals for any end point related to diabetes by category of updated mean haemoglobin A_{1c} concentration, adjusted for age, sex, and ethnic group, expressed for white men aged 50-54 years at diagnosis and with mean duration of diabetes of 10 years

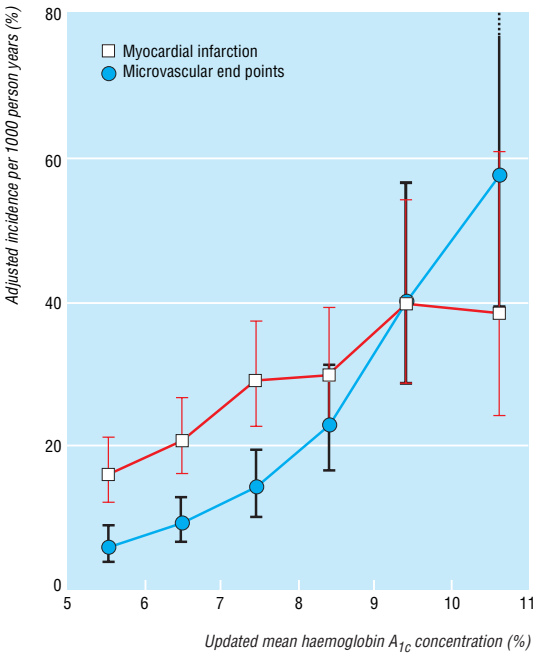

Fig 2 Incidence rates and 95% confidence intervals for myocardial infarction and microvascular complications by category of updated mean haemoglobin A_{1c} concentration, adjusted for age, sex, and ethnic group, expressed for white men aged 50-54 years at diagnosis and with mean duration of diabetes of 10 years

Results

The risk of each of the microvascular and macrovascular complications of type 2 diabetes and cataract extraction was strongly associated with hyperglycaemia as measured by updated mean haemoglobin A_{1c}. The incidence rates for any end point related to diabetes, adjusted for age, sex, ethnic group, and duration of diabetes, increased with each higher category of updated mean haemoglobin A_{1c}, with no evidence of a threshold and with a threefold increase over the range of updated mean haemoglobin A_{1c} of <6% (median 5.6%) to ≥10% (median 10.6%) (figs 1 and 2). The unadjusted and adjusted incidence rates are shown in table 2. Figure 2 shows the adjusted incidence rates for myocardial infarction and microvascular end points. The increase in the incidence rate for microvascular end points was greater over the range of increasing glycaemia than was the increase in the incidence rate for myocardial infarction. Thus at near normal concentrations of updated mean haemoglobin A_{1c} the risk of myocardial infarction was twice to three times that of a microvascular end point, whereas in the highest category of haemoglobin A_{1c} concentration (≥10%) the risks were of the same order.

Table 2 Incidence of complications in patients with type 2 diabetes by category of updated mean haemoglobin A_{1c} concentration (%). Rates per 1000 person years' follow up adjusted in Poisson regression model to white men aged 50 to 54 years at diagnosis of diabetes and followed up for 7.5 to <12.5 years, termed "10 years" (n=4585)

	<6%	6% to <7%	7% to <8%	8% to <9%	9% to <10%	≥10%
Aggregate end points						
Complications related to diabetes:						
Events/person years	229/9195	391/11 432	369/8464	268/5605	159/2542	88/1334
Unadjusted rate	24.9	34.2	43.6	47.8	62.5	65.9
Adjusted rate (95% CI)	35.9 (29.9 to 43.1)	48.7 (41.3 to 57.3)	65.5 (55.5 to 77.2)	74.5 (62.6 to 88.8)	103.2 (84.2 to 126.5)	124.9 (97.3 to 160.3)
Deaths related to diabetes:						
Events/person years	56/10 113	101/13 143	116/10 054	84/6595	47/3137	19/1537
Unadjusted rate	5.5	7.7	11.5	12.7	15.0	12.4
Adjusted rate (95% CI)	8.9 (6.3 to 12.7)	12.0 (8.9 to 16.3)	19.9 (14.8 to 26.7)	23.5 (17.2 to 32.0)	29.5 (20.4 to 42.6)	33.0 (19.8 to 55.1)
All cause mortality:						
Events/person years	112/10 113	207/13 143	188/10 054	123/6595	64/3137	26/1537
Unadjusted rate	11.1	15.8	18.7	18.7	20.4	16.9
Adjusted rate (95% CI)	17.0 (13.1 to 22.0)	23.3 (18.5 to 29.2)	30.0 (23.8 to 37.7)	31.8 (24.7 to 40.8)	37.0 (27.3 to 50.2)	40.7 (26.5 to 64.5)
Fatal or non-fatal myocardial infarction:						
Events/person years	100/9870	163/12 590	159/9579	101/6331	60/3016	23/1490
Unadjusted rate	10.1	13.0	16.6	16.0	19.9	15.4
Adjusted rate (95% CI)	16.0 (12.1 to 21.2)	20.8 (16.2 to 26.7)	29.2 (22.8 to 37.4)	30.0 (22.9 to 39.4)	39.6 (28.8 to 54.5)	38.6 (24.4 to 61.0)
Fatal or non-fatal stroke:						
Events/person years	32/9916	67/12 869	59/9822	32/6424	13/3062	9/1509
Unadjusted rate	3.2	5.2	6.0	5.0	4.2	6.0
Adjusted rate (95% CI)	4.3 (2.6 to 7.0)	6.6 (4.4 to 10.1)	8.3 (5.4 to 12.7)	7.4 (4.5 to 11.9)	6.7 (3.5 to 12.7)	12.0 (5.7 to 25.3)
Amputation or death from peripheral vascular disease:						
Events/person years	3/10 018	7/12 993	7/9897	9/6492	15/3061	7/1502
Unadjusted rate	0.3	0.5	0.7	1.4	4.9	4.7
Adjusted rate (95% CI)	1.2 (0.4 to 3.2)	1.2 (0.5 to 3.1)	2.6 (1.1 to 5.8)	4.0 (1.8 to 9.0)	10.9 (5.0 to 23.7)	12.2 (4.6 to 32.4)
Fatal or non-fatal microvascular disease:						
Events/person years	38/9814	77/12 707	86/9438	91/6185	73/2855	47/1432
Unadjusted rate	3.9	6.1	9.1	14.7	25.6	32.8
Adjusted rate (95% CI)	6.1 (4.1 to 9.0)	9.3 (6.7 to 12.9)	14.2 (10.3 to 19.5)	22.8 (16.7 to 31.3)	40.4 (28.9 to 56.5)	57.8 (39.3 to 85.1)
Single end points						
Heart failure:						
Events/person years	17/9967	34/12 928	36/9782	20/6432	10/3062	10/1514
Unadjusted rate	1.7	2.6	3.7	3.1	3.3	6.6
Adjusted rate (95% CI)	2.3 (1.2 to 4.5)	3.4 (1.9 to 5.8)	5.0 (2.9 to 8.6)	4.4 (2.4 to 8.2)	5.0 (2.3 to 10.6)	11.9 (5.5 to 25.8)
Cataract extraction:						
Events/person years	35/9841	59/12 763	49/9692	45/6355	19/3009	19/1495
Unadjusted rate	3.6	4.6	5.1	7.1	6.3	12.7
Adjusted rate (95% CI)	4.1 (2.5 to 6.5)	4.5 (3.0 to 6.9)	4.9 (3.1 to 7.6)	6.9 (4.4 to 10.8)	6.6 (3.8 to 11.6)	14.4 (8.1 to 25.7)

Person years, events, and unadjusted rates are for all patients.

The estimated hazard ratios associated with different categories of updated mean haemoglobin A_{1c} concentration, relative to the lowest category, are shown as log linear plots in figures 3 and 4. Mortality related to diabetes and all cause mortality were both strongly associated with glycaemia ($P<0.0001$). The risk of each of the complications evaluated rose with increasing updated mean haemoglobin A_{1c} concentration both before and after adjustment for baseline variables including age, sex, ethnic group, lipid concentrations, blood pressure, smoking, and albuminuria. The decrease in risk for each 1% reduction in updated mean haemoglobin A_{1c} concentration is shown in table 3 and figures 3 and 4. The glycaemia associated reduction in risk for microvascular end points and for amputation or death from peripheral vascular disease was greater (by 37% and 43% per 1% reduction in haemoglobin A_{1c} concentration, respectively, each $P<0.0001$) than it was for myocardial infarction, stroke, and heart failure (by 14% ($P<0.0001$), 12% ($P=0.035$), and 16% ($P=0.021$) per 1% haemoglobin A_{1c}, respectively) (fig 4). In models that included a variable for conventional control of blood glucose or intensive control with either sulphonylurea or insulin, updated mean haemoglobin A_{1c} remained associated with all complications, although for stroke and heart failure, where the numbers of events were lower than in the previous analyses, these were no longer significant. In these models, treatment of blood glucose per se had no association with any complication beyond that of mean updated haemoglobin A_{1c}.

There was no indication of a threshold for any complication below which risk no longer decreased nor a level above which risk no longer increased. The updated mean haemoglobin A_{1c} showed steeper relations than did baseline haemoglobin A_{1c} (table 3), and when both glycaemic variables were included in a model for all complications of diabetes only updated mean haemoglobin A_{1c} reached significance ($P<0.0001$).

Discussion

This observational analysis shows highly significant associations between the development of each of the complications of diabetes, including mortality, across the wide range of exposure to glycaemia that occurs in patients with type 2 diabetes. This association

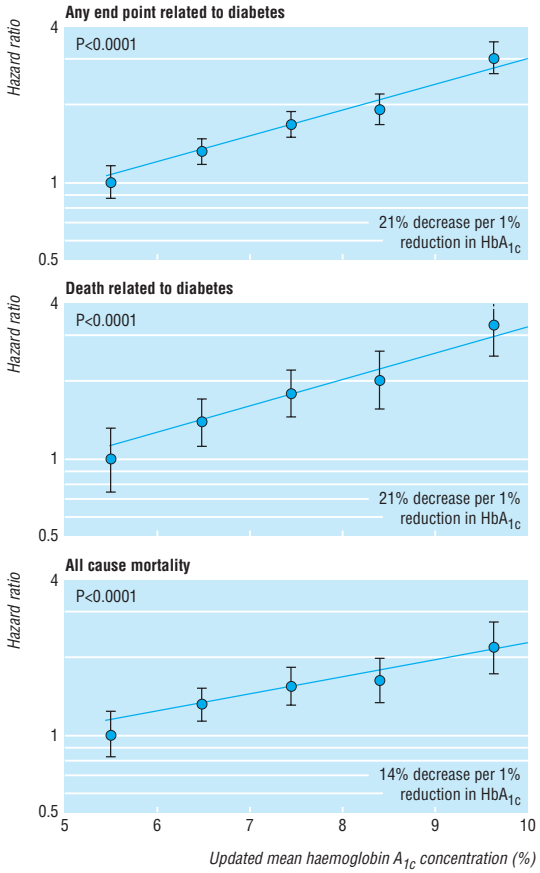

Fig 3 Hazard ratios, with 95% confidence intervals as floating absolute risks, as estimate of association between category of updated mean haemoglobin A_{1c} concentration and any end point or deaths related to diabetes and all cause mortality. Reference category (hazard ratio 1.0) is haemoglobin A_{1c} <6% with log linear scales. P value reflects contribution of glycaemia to multivariate model. Data adjusted for age at diagnosis of diabetes, sex, ethnic group, smoking, presence of albuminuria, systolic blood pressure, high and low density lipoprotein cholesterol, and triglycerides

remained after adjustment for other known risk factors, including age at diagnosis, sex, ethnic group, systolic blood pressure, lipid concentrations, smoking, and albuminuria. Each 1% reduction in haemoglobin A_{1c} was associated with a 37% decrease in risk for microvascular complications and a 21% decrease in the risk of any end point or death related to diabetes. The association with glycaemia was less steep for stroke and heart failure, for which blood pressure is a major contributing factor.[32 34 35] In patients within the lowest category of updated mean haemoglobin A_{1c} the incidence of myocardial infarction was higher than that of microvascular disease.[5] These results suggest that, in these people, the effect of hyperglycaemia itself may account for at least part of the excess cardiovascular risk observed in diabetic compared with non-diabetic people beyond that explained by the conventional risk factors of dyslipidaemia, hypertension, and smoking.[36] The rate of increase of relative risk for microvascular disease with hyperglycaemia was greater than that for myocardial infarction, which emphasises the crucial role of hyperglycaemia in the aetiology of small vessel disease and may explain the greater rate of microvascular complications seen in populations with less satisfactory control of glycaemia.

Relation to trial data

This observational analysis provides an estimate of the reduction in risk that might be achieved by the therapeutic lowering of haemoglobin A_{1c} by 1.0%, but it is important to realise that epidemiological associations cannot necessarily be transferred to clinical practice. Tissue damage from previous hyperglycaemia may not promptly be overcome, but the results are not inconsistent with those achieved by the policy of intensive glucose control in the clinical trial.[1] This suggests that the reduction in glycaemia obtained over a median 10 years of follow up of the trial, comparing median haemoglobin A_{1c} 7.0% with 7.9%, provided much of the benefit that could be expected from that degree of improved glycaemic control. Our results suggest that intensive treatment with sulphonylurea or insulin does not have an effect beyond that of lowering blood glucose concentration with respect to altering risk. The 16% risk reduction (P = 0.052) in myocardial infarction in the clinical trial in the group allocated to a policy of intensive blood glucose control (associated

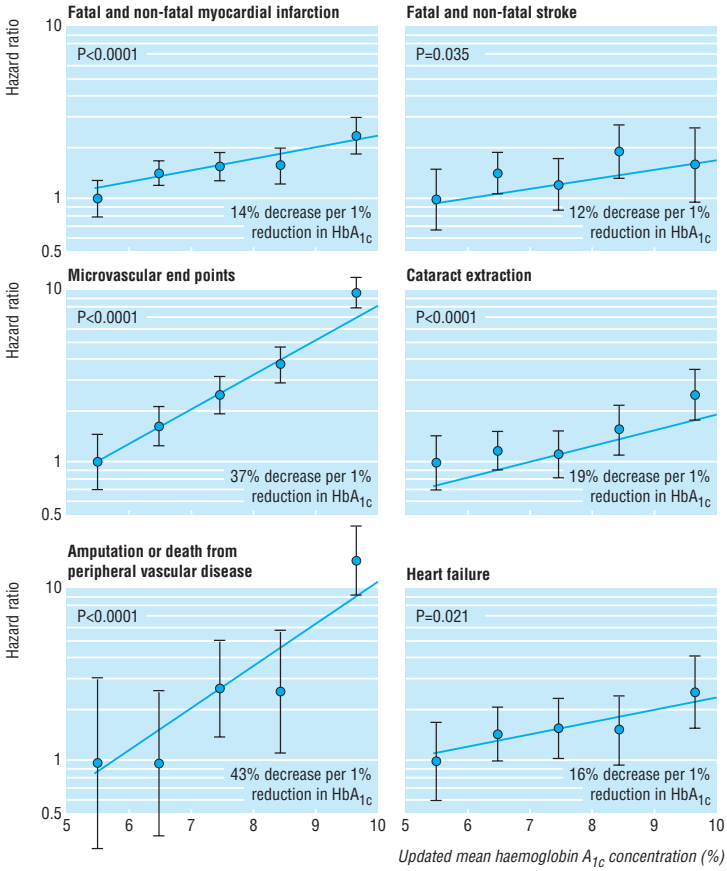

Fig 4 Hazard ratios, with 95% confidence intervals as floating absolute risks, as estimate of association between category of updated mean haemoglobin A_{1c} concentration and myocardial infarction, stroke, microvascular end points, cataract extraction, lower extremity amputation or fatal peripheral vascular disease, and heart failure. Reference category (hazard ratio 1.0) is haemoglobin A_{1c} <6% with log linear scales. P value reflects contribution of glycaemia to multivariate model. Data adjusted for age at diagnosis of diabetes, sex, ethnic group, smoking, presence of albuminuria, systolic blood pressure, high and low density lipoprotein cholesterol, and triglycerides

Table 3 Observational analysis of relation between glycaemic exposure and complications of diabetes as estimated by decrease in risk for 1% reduction in haemoglobin A_{1c} (HbA_{1c}) concentration, measured at baseline and as updated mean, controlled for age at diagnosis of diabetes, sex, ethnic group, smoking, albuminuria, systolic blood pressure, high and low density lipoprotein cholesterol, and triglycerides (n=3642) compared with results of clinical trial of intensive *v* conventional glucose control policy (n=3867)[1]

	Observational analysis					Clinical trial of intensive *v* conventional policy[1]		
	Baseline HbA_{1c}			Updated mean HbA_{1c}				
	No of events	Decrease in risk (%)/1% reduction (95% CI)	P value	Decrease in risk (%)/1% reduction (95% CI)	P value	No of events	Decrease in risk (%) seen for 0.9% difference in HbA_{1c} (95% CI)	P value
Aggregate end points								
Any end point related to diabetes	1255	11 (8 to 13)	<0.0001	21 (17 to 24)	<0.0001	1401	12 (1 to 21)	0.029
Deaths related to diabetes	346	9 (3 to 14)	0.0018	21 (15 to 27)	<0.0001	414	10 (–11 to 27)	0.34
All cause mortality	597	6 (2 to 10)	0.0081	14 (9 to 19)	<0.0001	702	6 (–10 to 20)	0.44
Myocardial infarction	496	5 (0 to 9)	0.067	14 (8 to 21)	<0.0001	573	16 (0 to 29)	0.052
Stroke	162	–4 (–14 to 6)	0.44	12 (1 to 21)	0.035	203	–11 (–49 to 19)	0.52
Peripheral vascular disease*	41	28 (18 to 37)	<0.0001	43 (31 to 53)	<0.0001	47	35 (–18 to 64)	0.15
Microvascular disease	323	23 (20 to 27)	<0.0001	37 (33 to 41)	<0.0001	346	25 (7 to 40)	0.0099
Single end points								
Heart failure	104	0 (–12 to 11)	0.99	16 (3 to 26)	0.016	116	9 (–35 to 39)	0.63
Cataract extraction	195	9 (2 to 16)	0.013	19 (11 to 26)	<0.0001	229	24 (0 to 42)	0.046

*Lower extremity amputation or fatal peripheral vascular disease.

with a 0.9% difference in haemoglobin A_{1c}) was similar to the 14% risk reduction seen in the epidemiological analysis, which was associated with a 1% reduction in concentration of updated mean haemoglobin A_{1c}. The UKPDS clinical trial evaluated a policy of intensive glucose control based primarily on single pharmacological treatments to enable evaluation of the individual treatments. Now that the UKPDS has shown that improved glucose control reduces the risk of complications and that the treaments used are safe in clinical practice, a larger reduction in haemoglobin A_{1c} might be achieved by the earlier use of combination treatments or by the use of newer treatments, which could further reduce the risk of myocardial infarction.

The observational analysis extends the range of hyperglycaemia studied in the UKPDS by including participants who, throughout the study, had near normal glucose concentrations on dietary treatment alone and participants who could never be treated by dietary treatment alone.[37] The UKPDS population was likely to be at lower risk of complications than other diabetic populations. Hence, the incidence rates we report are perhaps lower than might be observed in other diabetic populations as the cohort was newly diagnosed with diabetes, excluded old or ill patients, and contained a small proportion (6%) of participants with impaired fasting glycaemia.[38] None the less, the decrease in relative risk is unlikely to be different from other diabetic populations.

What is already known on this topic

The risk of developing complications of diabetes increases with increasing concentrations of hyperglycaemia

Reduction of hyperglycaemia in these individuals reduces the risk of complications

What this study adds

There is a direct relation between the risk of complications of diabetes and glycaemia over time

No threshold of glycaemia was observed for a substantive change in risk for any of the clinical outcomes examined

The lower the glycaemia the lower the risk of complications

The rate of increase of risk for microvascular disease with hyperglycaemia is greater than that for macrovascular disease

Lack of thresholds

We observed no thresholds of glycaemia for any type of complication of diabetes. This suggests that there is no specific target value of haemoglobin A_{1c} for which one should aim but that the nearer to normal the haemoglobin A_{1c} concentration the better. In reality, it is difficult to obtain and maintain near normal concentrations of haemoglobin A_{1c} in patients with type 2 diabetes, particularly in those with a high concentration of haemoglobin A_{1c} at diagnosis of diabetes.[37] Intensification of treatment by adding insulin to improve the relatively modest reduction in glycaemia achieved with oral hypoglycaemic treatments can be constrained by reluctance from patients and providers because, in part, of side effects such as hypoglycaemia or weight gain. These observational analyses, together with the results of the clinical trial, however, indicate that any improvement in a raised haemoglobin A_{1c} concentration is likely to reduce the risk of diabetic complications.

The magnitude of the risk reduction associated with a 1% reduction in haemoglobin A_{1c} concentration for myocardial infarction and microvascular disease (mostly retinopathy) was consistent with that observed in a cohort of patients from Wisconsin.[2] As in this analysis, a stronger association with haemoglobin A_{1c} concentration was observed for amputation than for ischaemic heart disease, possibly because glycaemia increases the risk of microvascular disease, neuropathy,

and peripheral arterial disease, each of which increases the risk of amputation.[4 8 18 39–41] The estimated 14% decrease in all cause mortality per 1% reduction in haemoglobin A_{1c} concentration was similar to that seen in other studies that have assessed glycaemia as haemoglobin A_{1c} as a continuous variable (per 1% change) in multivariate proportional hazards models.[9]

Summary

Both the observational and clinical trial analyses of an intensive glucose control policy suggest that even a modest reduction in glycaemia has the potential to prevent deaths from complications related to diabetes as cardiovascular and cerebrovascular disease account for 50-60% of all mortality in this and other diabetic populations.[8 42–47] Individuals with very high concentrations of glycaemia would be most likely to benefit from reduction of glycaemia as they are particularly at risk from the complications of type 2 diabetes, but the data suggest that any improvement in glycaemic control across the diabetic range is likely to reduce the risk of diabetic complications.

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Contributors: IMS selected the methodology, carried out the statistical analyses, coordinated the writing of the paper, and participated in the interpretation of results. AIA assisted with the writing of the paper and interpretation of results. HAWN, DRM, and DH participated in interpretation and revision of the paper. SEM managed the biochemical aspects and participated in interpretation and revision of the paper. CAC participated in preparation of the database and interpretation and revision of the paper. RCT and RRH were the principal investigators, planned and designed the study, and participated in interpretation and revision of the paper. RCT was also responsible for the initial draft of the paper. RRH is guarantor.

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Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study

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Abstract

Objective To determine the relation between systolic blood pressure over time and the risk of macrovascular or microvascular complications in patients with type 2 diabetes.
Design Prospective observational study.
Setting 23 hospital based clinics in England, Scotland, and Northern Ireland.
Participants 4801 white, Asian Indian, and Afro-Caribbean UKPDS patients, whether randomised or not to treatment, were included in analyses of incidence; of these, 3642 were included in analyses of relative risk.
Outcome measures Primary predefined aggregate clinical outcomes: any complications or deaths related to diabetes and all cause mortality. Secondary aggregate outcomes: myocardial infarction, stroke, lower extremity amputation (including death from peripheral vascular disease), and microvascular disease (predominantly retinal photocoagulation). Single end points: non-fatal heart failure and cataract extraction. Risk reduction associated with a 10 mm Hg decrease in updated mean systolic blood pressure adjusted for specific confounders
Results The incidence of clinical complications was significantly associated with systolic blood pressure, except for cataract extraction. Each 10 mm Hg decrease in updated mean systolic blood pressure was associated with reductions in risk of 12% for any complication related to diabetes (95% confidence interval 10% to 14%, $P<0.0001$), 15% for deaths related to diabetes (12% to 18%, $P<0.0001$), 11% for myocardial infarction (7% to 14%, $P<0.0001$), and 13% for microvascular complications (10% to 16%, $P<0.0001$). No threshold of risk was observed for any end point.
Conclusions In patients with type 2 diabetes the risk of diabetic complications was strongly associated with raised blood pressure. Any reduction in blood pressure is likely to reduce the risk of complications, with the lowest risk being in those with systolic blood pressure less than 120 mm Hg.

Introduction

The UK prospective diabetes study (UKPDS) has shown that a policy of tight control of blood pressure, which achieved a median blood pressure of 144/82 mm Hg compared with 154/87 mm Hg over median 8.4 years of follow up, substantially reduced the risk of microvascular disease, stroke, and deaths related to diabetes,[1] but not myocardial infarction. Complementary information for estimates of the risk of complications including myocardial infarction at different levels of blood pressure can be obtained from observational analysis of the UKPDS data. This information can help to estimate the expected reduction in the risk of diabetic complications from a given change in blood pressure. It can also help to assess whether or not thresholds in blood pressure exist below which the risk of complications is substantially reduced. Such thresholds would have substantial influence on the establishment of guidelines on clinical care.

People with type 2 diabetes have a greater incidence of cardiovascular disease, cerebrovascular disease, and renal disease than the general population. Epidemiological studies suggest that relative hyperglycaemia accounts for part but not all of the increased risk.[2–7] Raised blood pressure is more common in people with type 2 diabetes than in the general population,[8–12] and in people without diabetes it is a major risk factor for myocardial infarction and stroke.[13 14] Epidemiological studies of the role of blood

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Tissue-specific effects of sulfonylureas Lessons from studies of cloned K_{ATP} channels

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Abstract

Sulfonylureas stimulate insulin secretion in type-2 diabetic patients by blocking ATP-sensitive (K_{ATP}) potassium channels in the pancreatic β-cell membrane. This effect is mediated by the binding of the drug to the sulfonylurea receptor (SUR) subunit of the channel. K_{ATP} channels are also present in other tissues, but often contain different types of SUR subunits (e.g., SUR1 in β-cells, SUR2A in heart, SUR2B in smooth muscle). The sensitivity of these different types of K_{ATP} channels to sulfonylureas is variable: gliclazide and tolbutamide block the β-cell, but not the cardiac or smooth muscle, types of K_{ATP} channel. In contrast, glibenclamide blocks all three types of channel with similar affinity. The reversibility of the drugs also varies, with tolbutamide and gliclazide being reversible on all three types of K_{ATP} channel, while glibenclamide is reversible on cardiac, but not β-cell, K_{ATP} channels. This review summarizes current knowledge of how sulfonylureas act on the different types of K_{ATP} channel found in β-cells and in extrapancreatic tissues, and discusses the implications of these findings for their use as therapeutic agents.

Keywords: Tissue-specific; Sulfonylureas; K_{ATP} channels

1. K_{ATP} channels and insulin secretion

Sulfonylureas stimulate insulin secretion from pancreatic β-cells and are widely used in the treatment of type-2 diabetes mellitus. Their principal target is the ATP-sensitive potassium (K_{ATP}) channel (Ashcroft & Ashcroft, 1992), which plays a key role in insulin secretion both in response to sulfonylureas and to glucose (Ashcroft & Gribble, 1999; Ashcroft & Rorsman, 1989).

The K_{ATP} channels are located in the β-cell plasma membrane where they serve as gated pores that regulate the flow of K^+ ions into and out of the cell. In the unstimulated β-cell, the K_{ATP} channels are open and the outward movement of K^+ ions through the channel keeps the membrane potential at a negative level (−70 mV). When the plasma glucose concentration rises, the uptake and metabolism of the sugar by the β-cell increase, leading to closure of the K_{ATP} channels and depolarization of the β-cell membrane (Ashcroft et al., 1984). In turn, this triggers the opening of voltage-gated Ca^{2+} channels, eliciting Ca^{2+} influx and a rise in intracellular Ca^{2+} which stimulates the exocytosis of insulin-containing secretory granules. Sulfonylureas interact directly with the K_{ATP} channel to effect its closure and thereby initiate the same chain of events that culminates in insulin secretion.

In contrast to sulfonylureas, which bind directly to the channel and block its activity, glucose must be metabolized to cause K_{ATP} channel closure. It is currently thought that metabolic regulation is achieved by changes in the levels of the intracellular adenine nucleotides, ATP and MgADP. The former blocks channel activity, while the latter enhances the probability of channel opening (Cook & Hales, 1984; Kakei et al., 1986; Ashcroft & Gribble, 1999; Ashcroft & Rorsman, 1989). Thus when glucose is metabolized, producing a rise in ATP and a concomitant fall in MgADP, channel activity will be inhibited: conversely, when the metabolic rate is low, ATP will fall and MgADP will rise, thereby enhancing channel activity.

Recent studies have revealed that the β-cell K_{ATP} channel is an octameric 4:4 complex of two different kinds of protein subunit (Clement et al., 1997). One of these is an inwardly rectifying K-channel, Kir6.2, which acts as an ATP-sensitive K-channel pore (Inagaki et al., 1995; Sakura

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et al., 1995; Tucker et al., 1997). The other is a regulatory subunit, named the Sulphonylurea receptor (SUR), because of its ability to bind sulfonylurea drugs. This subunit not only endows Kir6.2 with sensitivity to sulfonylureas, but also confers sensitivity to the effects of MgADP and drugs like diazoxide, both of which stimulate K-channel channel opening (Aguilar-Bryan et al., 1995; Nichols et al., 1996; Gribble et al., 1997a; Tucker et al., 1997). Although the wild-type K_{ATP} channel requires both types of subunit (Kir6.2 and SUR1) to make a functional channel, a mutant form of Kir6.2 with a C-terminal truncation of 26 or 36 amino acids (Kir6.2ΔC) is capable of independent expression (Tucker et al., 1997). Kir6.2ΔC therefore provides a useful tool for studying the effects of drugs on the pore-forming subunit of the K_{ATP} channel.

2. Sulfonylurea block of the β-cell K_{ATP} channel

Sulfonylureas interact with the K_{ATP} channel at two sites: a low-affinity site that lies on Kir6.2 and a high-affinity site located on SUR1 (Gribble et al., 1997b). This was inferred from electrophysiological studies of the cloned channel, following expression of the mRNAs encoding wild-type or mutant subunits in *Xenopus* oocytes. Although the resulting K_{ATP} channels are largely blocked in the intact oocyte due to its high intracellular ATP concentration, they can be activated by metabolic inhibition or by excising a membrane patch into an intracellular solution free of nucleotides.

Fig. 1A (left) shows large currents recorded from a giant inside-out patch excised from a *Xenopus* oocyte expressing the wild-type β-cell K_{ATP} channel, Kir6.2/SUR1. Application of 100 μM tolbutamide produces ~ 50% block of the current, which is rapidly reversed when the drug is removed. The relationship between tolbutamide concentration and inhibition of the Kir6.2/SUR1 current is given in Fig. 1B. This is best fit by a two-site model with an IC_{50} of 2 μM for the high-affinity site and of 2 mM for the low-affinity site. To determine on which subunit the high- and low-affinity sites are located, the truncated Kir6.2 subunit (which is capable of independent expression) was studied in the absence of SUR1 (Gribble et al., 1997b). Fig. 1 shows that this is blocked by tolbutamide with low affinity, the IC_{50} being close to that observed for the low-affinity site on the wild-type (Kir6.2/SUR1) channel. Thus, the low-affinity site is located on Kir6.2 and the high-affinity site on SUR1.

Similar results are found for glibenclamide and for the benzoic acid derivative, meglitinide (Gribble et al., 1998). Like tolbutamide, both drugs interact with a low-affinity site on Kir6.2 and a high-affinity site on SUR1. However, they are significantly more potent than tolbutamide: the IC_{50} for the high-affinity site was 4 nM for glibenclamide, 300nM for meglitinide and 2 μM for tolbutamide (Gribble et al., 1998). All three drugs also produced low-affinity block of Kir6.2. Low-affinity block is unlikely to be of clinical significance, however, because plasma concentrations of

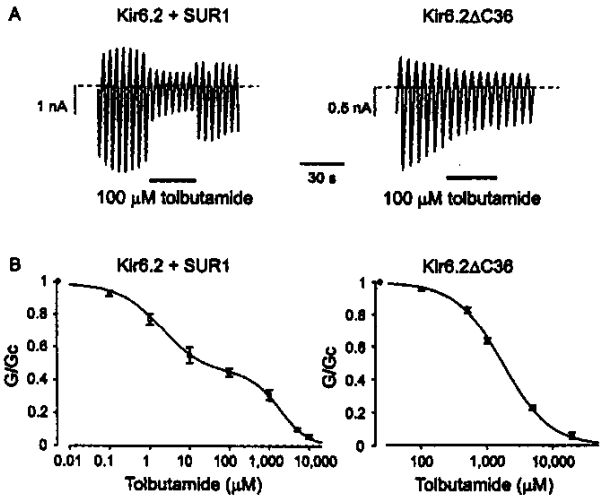

Fig. 1. Tolbutamide interacts with two sites on the β-cell K_{ATP} channel, a high-affinity site on SUR1 and a low-affinity site of Kir6.2. (A) Effect of tolbutamide (0.1 mM) on the β-cell K_{ATP} channel (Kir6.2/SUR1, left), and on the truncated Kir6.2 subunit (Kir6.2ΔC36) expressed in the absence of SUR (right). From Gribble et al. (1997b). (B) Dose–response relationships for tolbutamide block of Kir6.2/SUR1 (left) and Kir6.2ΔC36 (right) currents. The conductance in the presence of the sulphonylurea (G) is expressed as a fraction of that in the absence of the drug (G_c) (vertical axis) and plotted against the drug concentration (horizontal axis). *Xenopus* oocytes were co-injected with mRNAs encoding either Kir6.2 plus SUR1 or Kir6.2ΔC36, and macroscopic currents were recorded from inside-out patches in response to a series of voltage ramps from −110 to +100 mV. From Gribble et al. (1997b).

these drugs in diabetic patients do not reach such high levels (Sartor et al., 1980a,b). It is their interaction with the high-affinity site that is responsible for the therapeutic effects of sulfonylurea drugs.

High-affinity inhibition by tolbutamide (and other sulfonylureas) blocks only about 60% of the total current in excised membrane patches. The story is different in intact cells, however, where saturation of the high-affinity site produces complete block of the channel (Trube et al., 1986). This is due to the presence of intracellular MgADP which produces an apparent enhancement of sulfonylurea inhibition (Zünkler et al., 1988). The evidence suggests that this may result because sulfonylureas abolish the stimulatory action of MgADP (which is mediated via SUR1), without affecting the ability of the nucleotide to interact with the ATP-binding site on Kir6.2 and cause channel inhibition (Gribble et al., 1997b). Inhibition in the presence of MgADP and tolbutamide is thus due to the combined actions of the drug and nucleotide.

3. Tissue-specific effects of sulfonylureas

K_{ATP} channels are found at high density in a variety of cell types other than the β-cell, including cardiac,

smooth and skeletal muscle, and some brain neurons. Although their roles in extrapancreatic tissues are less well characterized, they are thought to couple cell metabolism to membrane excitability and, in some tissues, to mediate the actions of hormones and transmitters. In the heart, K_{ATP} channels are normally closed and open only in response to metabolic stress, such as that which occurs during ischemia (Nichols & Lederer, 1991). This produces shortening of the cardiac action potential. In skeletal muscle, they contribute to the enhanced K^+ efflux and fatigue found during severe exercise (Davis et al., 1991). They are also important in the control of vascular smooth muscle tone, and therefore of blood pressure (Quayle et al., 1997). Their physiological role in neurons is not clearly established, but it is believed that they regulate synaptic transmitter release and that they may be involved in the response to cerebral ischemia or glucose deprivation (Schmid-Antomarchi et al., 1990; Heurteax et al., 1993). Clearly, it is important to determine the extent to which K_{ATP} channels are open under physiological conditions in all these tissues, because this will influence whether or not sulfonylureas will have any extrapancreatic effects.

K_{ATP} channels in different tissues usually share a common Kir6.2 subunit, although they may possess different types of SUR subunit (Ashcroft & Gribble, 1999). The β-cell K_{ATP} channel is composed of Kir6.2 and SUR1, the cardiac type of Kir6.2 and SUR2A, and the smooth muscle type, probably, of Kir6.2 and SUR2B. Both Kir6.2/SUR1 and Kir6.2/SUR2B combinations are found in the brain. An additional type of K_{ATP} channel is found in the mitochondria (Garlid, 1996), but its molecular identity remains unknown. It is to be hoped that it will be cloned soon, because this channel has been implicated in the process of ischemic preconditioning.

3.1. Tolbutamide and gliclazide

A number of studies suggest that the different types of K_{ATP} channel exhibit different specificities towards the various sulfonylureas. In particular, tolbutamide inhibits the β-cell (Kir6.2/SUR1), but not the cardiac (Kir6.2/

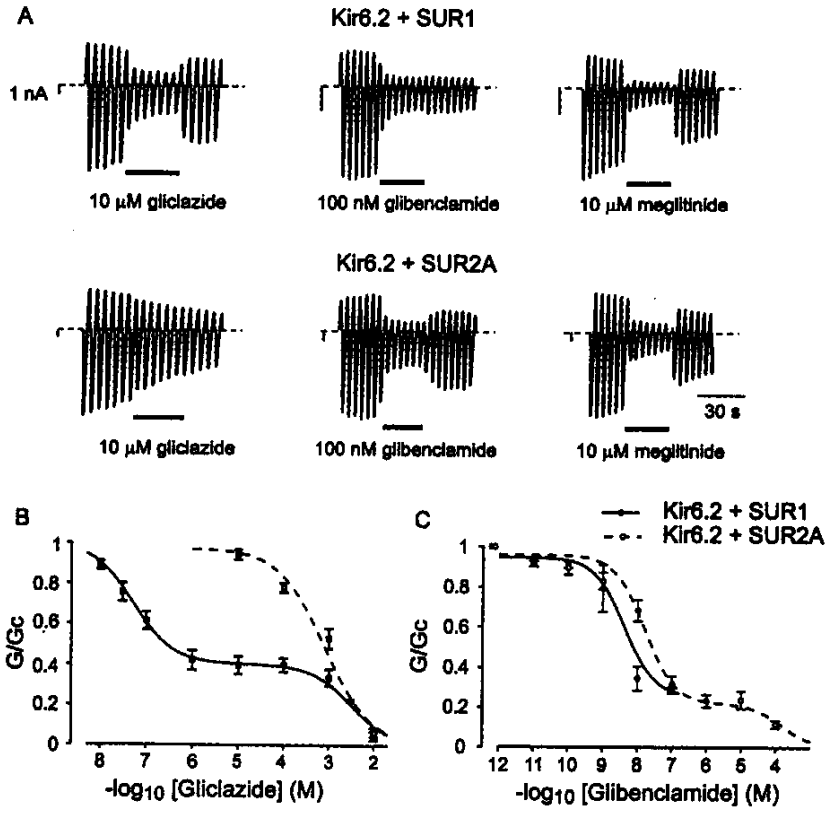

Fig. 2. Gliclazide blocks β-cell, but not cardiac, K_{ATP} channels with high affinity, while glibenclamide blocks both types of channel. (A) Effects of gliclazide (10 μM), glibenclamide (100 nM) or meglitinide (10 μM) on cloned β-cell (Kir6.2/SUR1) and cardiac (Kir6.2/SUR2A) K_{ATP} currents. From Gribble et al. (1998) and Gribble & Ashcroft (1999). (B, C) Dose–response relationships for gliclazide (B) and glibenclamide (C) inhibition of Kir6.2/SUR1 and Kir6.2/SUR2A currents. The conductance in the presence of the sulphonylurea (G) is expressed as a fraction of that in the absence of the drug (G_c). Oocytes were co-injected with mRNAs encoding Kir6.2 and either SUR1 or SUR2A, and macroscopic currents recorded from inside-out patches in response to a series of voltage ramps from −110 to +100 mV. From Venkatesh et al. (1991) and Gribble et al. (1998) and Gribble & Ashcroft (1999).

SUR2A) type of K_{ATP} channel with high affinity, suggesting that SUR2A does not possess a high-affinity binding site for tolbutamide (Venkatesh et al., 1991; Gribble et al., 1998). Similar results are found for gliclazide (Gribble & Ashcroft, 1999). Fig. 2 shows the dose–response curves for gliclazide inhibition of cloned β-cell and cardiac K_{ATP} channels. Whereas gliclazide produces both high- and low-affinity block of Kir6.2/SUR1 currents, a single, low-affinity site is observed for Kir6.2/SUR2A currents. Low-affinity inhibition of both types of channel is similar to that found when Kir6.2ΔC36 is expressed in the absence of SUR (Gribble et al., 1997b). This suggests that, like tolbutamide, gliclazide interacts with high affinity with SUR1 but not SUR2A. However, gliclazide is much more potent than tolbutamide: the IC_{50} is ~ 50 nM for gliclazide compared with ~ 2 μM for tolbutamide. Because the only structural difference between these drugs is the 3-amino-aza [3.3.0] octane ring of the gliclazide molecule, this group is likely to be involved in high-affinity binding to SUR1. Like tolbutamide block, that produced by gliclazide is rapidly reversed.

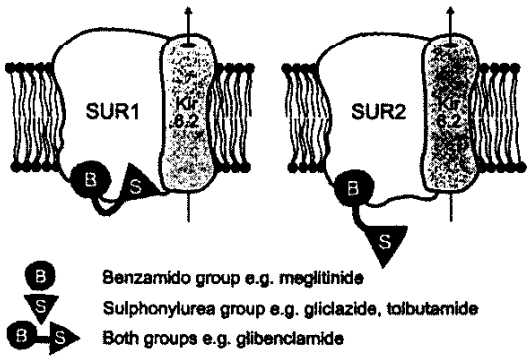

Fig. 3. Model for sulfonylurea interaction with β-cell and cardiac K_{ATP} channels. K_{ATP} channels containing the β-cell SUR1 possess two high-affinity sites, one that accepts sulfonylureas (e.g., tolbutamide, gliclazide) and one that accepts benzamido compounds (e.g., meglitinide), whereas those containing the cardiac SUR2A possess only the benzamido site. Because glibenclamide possesses both sulfonylurea and benzamido moieties, it interacts with SUR1 at two sites, but only with a single site on SUR2A. Consequently, drug inhibition of Kir6.2/SUR1 currents reverses more slowly than that of Kir6.2/SUR2A currents. From Ashcroft & Gribble (1999).

3.2. Meglitinide

Meglitinide is not a sulfonylurea but a benzamido derivative, equivalent to the non-sulphonylurea moiety of glibenclamide. This drug mediates reversible high-affinity inhibition of both the β-cell and cardiac types of K_{ATP} channel (Gribble et al., 1997b) (Fig. 2A). The affinity of this block is similar for the two types of SUR, the IC_{50} being ~ 0.3 μM for Kir6.2/SUR1 and ~ 0.5 μM for Kir6.2/SUR2A currents. This suggests that both SUR1 and SUR2A may possess a benzamido-binding site.

3.3. Glibenclamide and glimepiride

Glibenclamide blocks both β-cell and cardiaccloned K_{ATP} channels with high affinity (Fig. 2A,C). The IC_{50} for Kir6.2/SUR1 and Kir6.2/SUR2A currents were ~ 4 and ~ 27 nM, respectively (Gribble et al., 1998), and similar values have been reported for native channels. In preliminary studies, we find that glimepiride behaves like glibenclamide and blocks both the cloned β-cell and cardiac K_{ATP} channel with about the same high affinity (Song and Ashcroft, unpublished observations). Because glibenclamide and glimepiride contain both sulfonylurea and benzamido moieties, it is possible that these drugs bind simultaneously to both tolbutamide and benzamido-binding sites of SUR1, but only to the benzamido-binding site on SUR2A (Ashcroft & Gribble, 1999) (Fig. 3). This idea can also explain why the glibenclamide (and glimepiride) block of Kir6.2/SUR1 channels is poorly reversible (and not detectable on the time scale of electrophysiological experiments), whereas the glibenclamide block of Kir6.2/SUR2A currents is rapidly reversed. If glibenclamide binds to both sulfonylurea and benzamido sites on SUR1, the drug would only dissociate when it unbinds simultaneously from both sites. This is likely to occur with a low probability, accounting for the poor reversibility of the drug. In contrast, if the drug interacts with a single (benzamido) site on SUR2A, it will unbind readily and its effect be more easily reversed.

In intact cells, the effect of sulfonylureas on Kir6.2/SUR1 currents is enhanced by the presence of MgADP, as described above. In contrast, MgADP reduces glibenclamide block of Kir6.2/SUR2A currents, so that the sulfonylurea is less effective on cardiac K_{ATP} channels in intact cells (Venkatesh et al., 1991; Gribble et al., 1998). This has important implications because it means that under physiological conditions, sulfonylureas are likely to be much less effective on cardiac K_{ATP} channels than on those of β-cells.

4. Clinical implications

Since K_{ATP} channels are found in a wide variety of extrapancreatic tissues (cardiac, skeletal and smooth muscle, and neurons), drugs which cross-react with different members of the K_{ATP} channel family have the potential to cause undesired side effects. Thus, the finding that some sulfonylureas (e.g., tolbutamide, gliclazide) show differential sensitivity towards the β-cell, cardiac, and smooth muscle types of K_{ATP} channel raises the question of whether these might have greater therapeutic value in type-2 diabetes than sulfonylureas that interact with all three types of channel (e.g., glibenclamide).

The most significant of any putative side effects is likely to be that on cardiac muscle. However, because cardiac K_{ATP} channels are thought to be closed under physiological conditions and to open only in response to

ischemic stress (Nichols & Lederer, 1991), glibenclamide is likely to be without effect in patients without cardiac disease. Furthermore, the efficacy of sulfonylureas is markedly reduced by intracellular MgADP (Venkatesh et al., 1991; Gribble et al., 1998), so that even at therapeutic concentrations, the drug may not completely block ischemic activation of K_{ATP} channels. Indeed, the UK Prospective Diabetes Study (UKPDS) (1998) found no difference in the mortality, or diabetic end points, of patients treated with insulin, glibenclamide, or chlorpropamide. It is worth pointing out, however, that in this study, patients treated with glibenclamide who were moved subsequently onto insulin therapy were still counted as glibenclamide-treated. It is therefore difficult to determine from the UKPDS whether or not glibenclamide has any detrimental effects in patients with cardiac disease. What is required is a careful comparison of cardiac morbidity in type-2 diabetic patients with ischemic heart disease treated with insulin, glibenclamide, or gliclazide.

Acknowledgments

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Gliclazide Modified Release: A Critical Review of Pharmacodynamic, Metabolic, and Vasoprotective Effects

Guntram Schernthaner

Gliclazide modified release (MR) is a new formulation of the drug gliclazide and is given once daily. The specifically designed hydrophilic matrix of gliclazide MR leads to a progressive drug release that parallels the 24-hour glycemic profile in type 2 diabetic patients. Development studies showed a sustained efficacy over 2 years coupled with a very good acceptability. Gliclazide MR acts selectively on adenosine triphosphate–dependent potassium (K_{ATP}) channels of the pancreatic β cell. No interaction with cardiovascular K_{ATP} channels has been shown, indicating that the drug can be safely used in patients with ischemic heart disease. In addition, gliclazide MR shows the ability to inhibit key mechanisms in diabetic angiopathy, independently of glycemic control.

THE UNITED KINGDOM Prospective Diabetes Study (UKPDS) has confirmed the need for improved long-term glycemic control to reduce patient risk for diabetic vascular complications.[1] Guidelines for the management of type 2 diabetes advocate a multiple risk factor approach, aimed at treating the disease and minimizing other cardiovascular risk factors, such as hypertension and dyslipidemia.[2] Multifactorial intervention should begin with lifestyle modifications and exercise, but in many patients this inevitably implies drug therapy.[3] Sulfonylureas have been used successfully for the treatment of type 2 diabetes for almost 40 years and have been recommended as first-line therapy in patients with useful islet β-cell function in whom dietary and lifestyle modifications have proved to be insufficient.[2] A multifactorial, target-driven long-term therapeutic intervention including aggressive lowering of lipids (mainly by statins), blood pressure (mainly by angiotensin-converting enzyme [ACE] inhibitors), and blood glucose can significantly reduce the risk for cardiovascular disease, diabetic nephropathy, and diabetic retinopathy by 50% to 60% in hypertensive type 2 diabetic patients with microalbuminuria.[4] Treatment to all the recommended targets is a considerable challenge both for physicians and for patients, who may easily find themselves on treatment regimens involving half a dozen or more different drugs. A rational treatment approach will hence consider the simplicity of drug administration, as well as the mechanism of action and efficacy/acceptability profile.

GLICLAZIDE MODIFIED RELEASE: AN INNOVATIVE ONCE-DAILY USE SULFONYLUREA

Gliclazide modified release (MR) is a new once-daily formulation of the sulfonylurea gliclazide. This new preparation employs a hydrophilic matrix of a hypromellose-based polymer that expands to form a gel when in contact with gastrointestinal fluid, which progressively releases gliclazide.[5] The bioavailability after administration of a single dose of 30 mg is almost complete (97%).[6] The release of gliclazide over a 24-hour period has been shown to parallel the circadian glycemic profile of type 2 diabetics[6] (Fig 1). Consistent with this release profile, the efficacy of gliclazide MR was shown to be balanced over 24 hours in a short-term study including 21 patients.[8] After 10 weeks on gliclazide MR, fasting and postprandial plasma glucose values were decreased by 2.63 and 3.03 mmol/L, respectively. Figure 2 shows the glycemic profiles before and after treatment with gliclazide MR.

It has been well established that a once-daily dosing regimen is crucial for achieving optimal compliance and hence helps to achieve long-term glycemic control.[10] A recent publication reported that hemoglobin A_{1c} (HbA_{1c}) levels were strongly correlated with dosing frequency of oral antidiabetics, a low dosing frequency being associated with better metabolic control. In this study, mean HbA_{1c} was 1.4% lower in the group of patients with optimal compliance relative to the group with the worst compliance.[11]

LONG-TERM CLINICAL EFFICACY

The clinical efficacy of gliclazide MR has been investigated in several clinical trials. In a large 12-month randomized study, patients that were previously treated by diet or with up to 2 oral antidiabetic drugs were randomized to gliclazide MR or gliclazide 80 mg. In patients who had been suboptimally controlled on diet, HbA_{1c} improved by a mean of 0.9%. This improvement was sustained during the treatment period, these patients ending the study with a mean HbA_{1c} of 7.3%. In those patients previously treated with one oral antidiabetic agent, the glycemic control remained stable on gliclazide MR monotherapy. Despite the heterogeneous study population, 55% of the patients were controlled on the lowest dosages of gliclazide MR. Five hundred forty-nine of the patients were subsequently enrolled in a 12-month additional treatment period on gliclazide MR alone or in combination according to their glycemic control, in conditions encountered in routine medical practice. The results over the total 24-month period confirmed the sustained efficacy of gliclazide MR. HbA_{1c} was significantly reduced by 0.95% and 0.33% from baseline in patients previously treated with diet alone or with one oral antidiabetic agent. Gliclazide MR used in monotherapy or in combination with one other oral antidiabetic agent reduced HbA_{1c} to a similar extent.[12]

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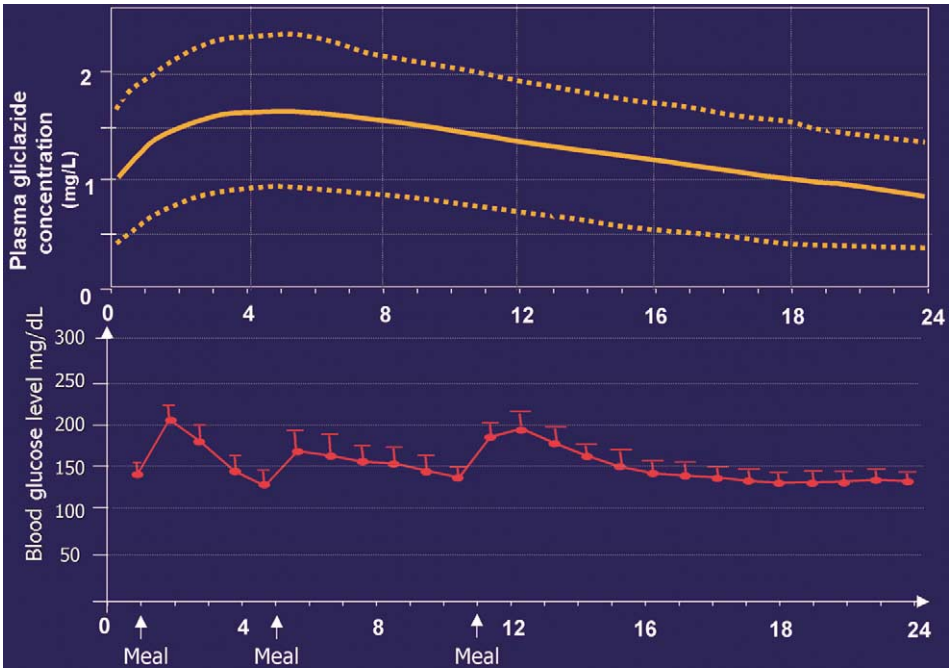

Fig 1. Twenty-four–hour profile of release of active ingredient (1) and typical 24-hour glycemic profile of untreated type 2 diabetic patients (2). (1) Adapted from Francillard et al[6]; (2) Reprinted with permission from Reaven et al.[7]

TOLERABILITY IN A DIVERSIFIED POPULATION

The tolerability of gliclazide MR was observed during an extensive phase III development program. In the 12-month, randomized, double-blind study described above, few adverse events were reported, with arthralgia (3.4%), arthritis (2.8%), back pain (3.4%), and bronchitis (4.9%) being the most common.[12,13] It is of particular interest that body weight remained stable, whereas significant weight gain is usually described during long-term treatment with sulfonylureas (Fig 3).

A very low incidence of hypoglycemia has been documented for gliclazide MR.[9,12,13] Mild to moderate symptoms suggestive of hypoglycemia were observed in approximately 5% of patients, whereas no nocturnal episodes or episodes of severe hypoglycemia were reported. In the elderly subpopulation (39% of patients were over 65 years, 45% of whom had impaired renal function), a lower rate of symptoms suggestive of hypoglycemia was observed in 1.4% of patients. The pattern of hypoglycemia was comparable in patients with renal insufficiency ($20 < \text{creatinine clearance} < 80$ mL/min) and in the whole population.

PHYSIOLOGICAL INSULIN SECRETION, EFFECTS ON INSULIN SENSITIVITY, AND POTENTIAL PROTECTION OF β CELLS

Normal insulin secretion to a glucose stimulus is biphasic with a first phase of insulin release within the first 10 minutes, followed by a progressive second phase.[15] In many type 2 diabetics, this first phase of insulin secretion, which limits the prandial rise in glycemia and primes insulin-target tissues, is attenuated.[15] Loss of the first phase of insulin secretion causes

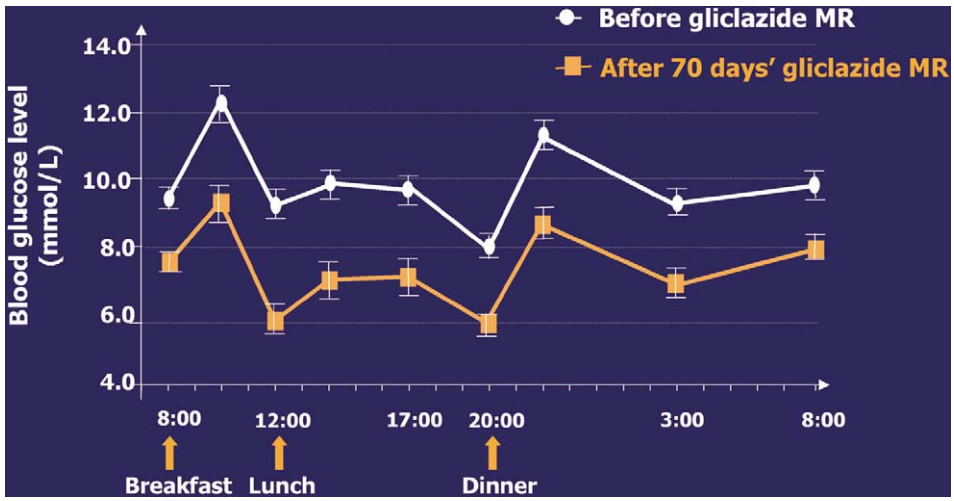

Fig 2. Twenty-four–hour blood glucose profile before and after administration of gliclazide MR. Reprinted with permission from Guillausseau and Greb.[9] © Masson Editeur.

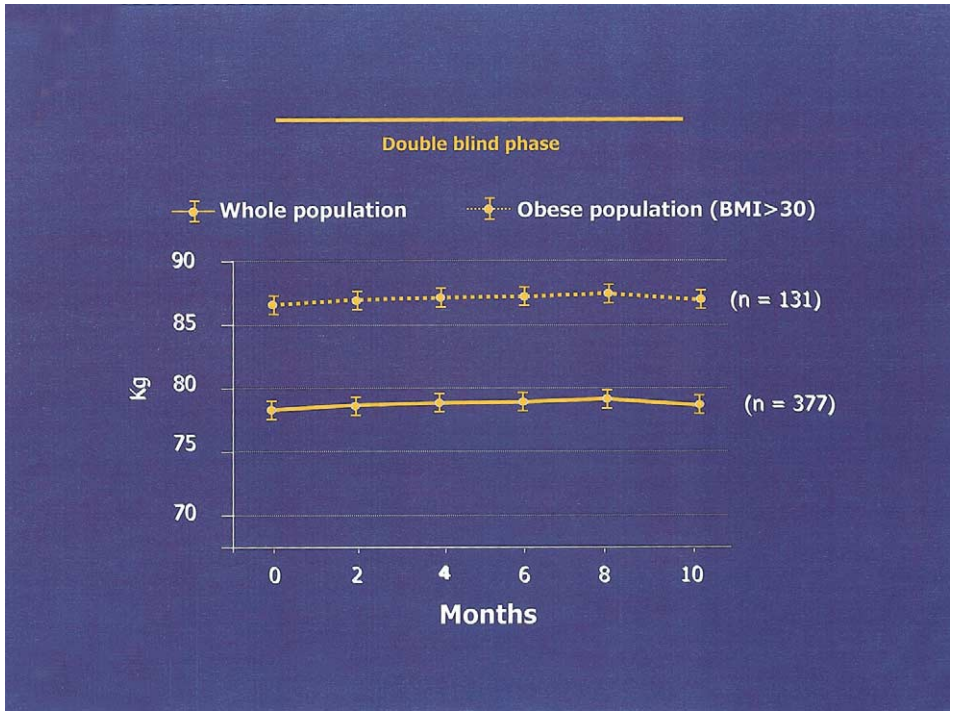

Fig 3. Absence of effect on weight on gliclazide MR in the general type 2 diabetic population and an obese population (body mass index > 30 kg/m^2) over 10 months' treatment. Reprinted with permission from Drouin.[13]

delayed, excessive insulin secretion in the late prandial phase, which has pathogenic consequences, including weight gain.[16] Clinical studies[17] and clamp experiments[18] in type 2 diabetes patients illustrate that gliclazide does induce substantial first-phase insulin release. After 6 months of gliclazide treatment in diet-uncontrolled type 2 diabetic patients, the difference in the initial insulin peak from the pretreatment was striking, but still lower than the insulin response of nondiabetic subjects.[17] In lean patients with more advanced type 2 diabetes, Ligtenberg et al[19] could only find an insignificant increase in first-phase insulin release with gliclazide. These discrepant findings[16-19] might be explained by the progressive loss of β-cell function with increasing diabetes duration as demonstrated in the UKPDS.[20] However, the methodology and conclusions of this study were criticized by Cerasi.[21] Further clinical studies should therefore be undertaken to investigate the effect of different sulfonylureas on the first phase of insulin secretion in patients with various degree of β-cell failure.

Gliclazide treatment also increases insulin sensitivity.[22] It has been shown that glucose uptake into perfused rat skeletal muscle obtained from streptozotocin-diabetic rats treated with gliclazide 5 mg/kg twice daily for 12 days increased 2-fold under insulin-stimulated conditions, compared with untreated controls.[23] It has also been shown that gliclazide potentiates the suppression of hepatic glucose production in type 2 diabetic patients during hyperglycemia elicited by an isoglycemic clamp. As this suppression seems independent of the action of the drug on pancreatic hormones, it is postulated that gliclazide exerts a direct effect on liver glucose metabolism.[24] Thus, the improved insulin sensitivity in liver and skeletal muscle with gliclazide treatment can be linked to a direct effect and is not simply due to increased insulin secretion or reduced glucose toxicity with improved glycemic control.[24]

Recently, it has been discovered that susceptibility of pancreatic β cells to oxidative stress contributes to the progressive deterioration of β-cell function in type 2 diabetes. Very recently, Kimoto et al[25] investigated whether gliclazide could protect pancreatic β cells from oxidative damage. The authors demonstrated that gliclazide but not glibenclamide protected MIN6 cells from the cell death induced by H_2O_2. The interesting data suggest that gliclazide may be effective in protecting β cells from the toxic action of reactive oxygen species in diabetes.

β-CELL SELECTIVITY AND REVERSIBLE BINDING TO THE SULFONYLUREA RECEPTOR

Sulfonylureas stimulate insulin secretion by inhibiting ATP-sensitive potassium (K_{ATP}) channels in pancreatic β cells. It is now well established that these channels consist of a regulatory sulfonylurea receptor (SUR) and a pore-forming subunit (Kir).[26] K_{ATP} channels composed of different sulfonylurea receptor isoforms have been described in a variety of tissues outside the pancreas.[26] They are found in high density in cardiac, smooth, and skeletal muscle, raising the question of whether sulfonylureas can potentially increase cardiovascular risk. To address this question, the selectivity for pancreatic β cells of different sulfonylureas has been investigated in cloned β-cell (Kir6.2.SUR1), cardiac (Kir6.2/SUR2A), and vascular smooth muscle (Kir6.2/SUR2B) K_{ATP} receptors, expressed in *Xenopus* oocytes.[27,28] In this model, gliclazide has been shown to bind selectively to the β-cell K_{ATP} channels only, whereas glibenclamide and glimepiride at therapeutic concentrations show significant action on the cardiovascular channels[29] (Fig 4). Moreover, glimepiride and glibenclamide impair the ability of nicorandil, a K_{ATP} channel opener and antianginal agent, to

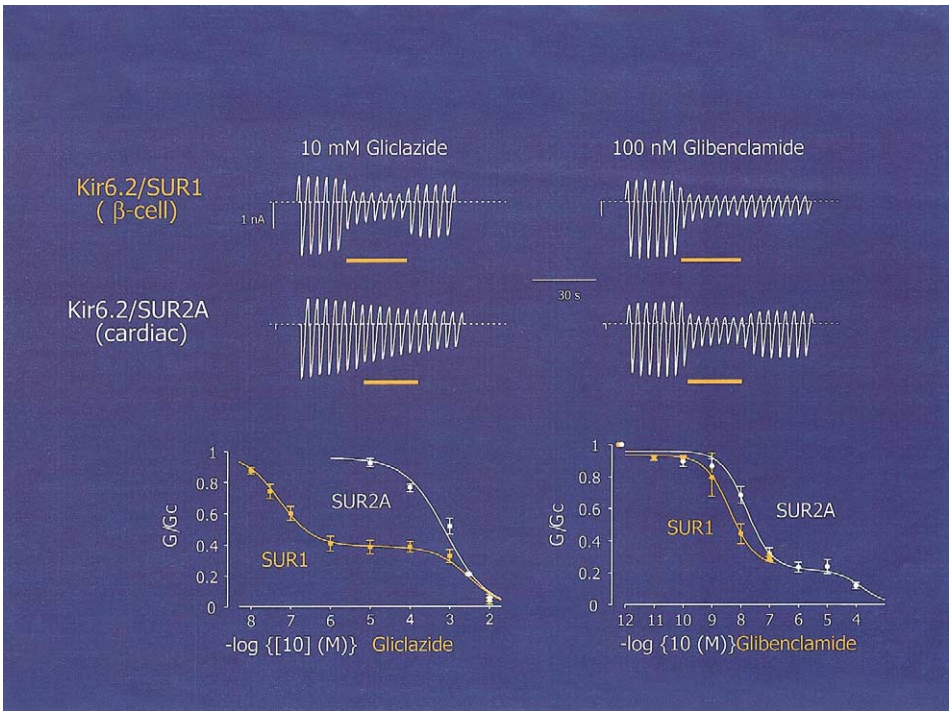

Fig 4. Different inhibition of β-cell (Kir 6.2/SUR 1) and cardiac (Kir 6.2/SUR2A) types of K_{ATP} channel by gliclazide and glibenclamide. Macroscopic currents are recorded in response to a series of voltage ramps from −110 mV to +100 mV. Reprinted with permission from Gribble and Ashcroft[27] (© 1999 by Springer-Verlag) and Gribble et al[28] (Copyright © 1998 American Diabetes Association. From Diabetes, Vol. 47, 1998; 1412-1419. Reprinted with permission from *The American Diabetes Association*.)

open cloned cardiac SUR2A and smooth muscle SUR2B channels in this model, whereas gliclazide showed no interaction.[30] These results were confirmed in intact vessels where Ravel et al showed that K_{ATP} channel–mediated vasodilation was not blocked in vitro in the guinea pig and rat aorta, or in vivo in hamster cheek pouch microvessels by gliclazide, but was strongly inhibited by glibenclamide and glimepiride at therapeutic concentrations.[32] Finally, a recent study showed in type 2 diabetic patients that chronic treatment with gliclazide in contrast to glibenclamide did not reduce post-ischemic reactive hyperemia. The investigators concluded that this is probably based on different binding towards SUR receptors.[33] These results provide consistent evidence that there is no cardiovascular action of the gliclazide molecule, supporting its cardiovascular safety.

The binding of gliclazide to sulfonylurea receptors on pancreatic β cells is very rapidly reversible in contrast to glibenclamide and glimepiride, which show prolonged binding to the pancreatic β cell.[27,28] This property may contribute to explaining the low rate of hypoglycemia and pancreatic exhaustion, hence secondary failure, of gliclazide MR in comparison to sulfonylureas that remain bound to the pancreatic receptor for a longer period.[5]

BENEFICIAL EFFECT ON ENDOTHELIAL DYSFUNCTION

Oxidative stress, in particular the oxidation of low-density lipoprotein (LDL), is increasingly acknowledged as a key step in the pathophysiology of vascular disease. Advanced glycation end product (AGE) deposition has been closely linked to endothelial dysfunction.[33] Moreover, hypercoagulability has been widely documented in type 2 diabetic patients and associated with both microvascular and macrovascular disease.[34,35]

Gliclazide MR differs from other sulfonylureas in that is has glucose-lowering independent vascular properties, which have been extensively studied. The unique feature of the gliclazide molecule is its azabicyclo-octyl ring, grafted to a sulfonylurea group. It is hence suggested that this feature is responsible for the ability of gliclazide MR to reduce oxidative stress at therapeutic concentrations, a property not shared by glibenclamide.[36] It has been shown that the effect of gliclazide is as pronounced as that of the reference antioxidant vitamin C.[37] Type 2 diabetic patients treated for 10 months with gliclazide MR showed significant improvement in the key parameters for oxidative stress (total plasma antioxidant capacity, concentration of thiols, superoxide dismutase, and isoprostanes), independently of glycemic control.[37] Other investigators showed that gliclazide decreased monocyte adhesion to the endothelium induced by oxidized LDL.[38] Similarly, glucose-mediated adhesion of neutrophils to endothelial cells and increased expression of E selectin, vascular cell adhesion molecule–1 (VCAM-1), and intercellular adhesion molecule–1 (ICAM-1) by endothelial cells were significantly inhibited by coincubation with gliclazide, but not glibenclamide, nateglinide, glimepiride, or metformin.[39] More recent data suggest that gliclazide inhibits high glucose-mediated neutrophil–endothelial cell adhesion and expression of endothelial adhesion molecules through inhibition of a protein kinase C pathway.[40] A recent study in type 2 diabetic patients showed that gliclazide, unlike glibenclamide, improves total radical antioxidant parameter (TRAP), plasma lipid peroxides, and endothelium-dependent vasodilation induced by L-arginine. These effects were independent of glycemic control after a treatment period of 12 weeks.[41] Furthermore, gliclazide reduces hypercoagulability in type 2 diabetic patients by reduction in platelet overactivity[42] and enhances fibrinolysis.[43] The anti-aggregatory platelet ac-

tivity is not restricted to gliclazide, but has been recently also shown for other sulfonylureas.[44] Quantitative structure-activity relationships indicate that the anti-aggregatory platelet activity is mainly affected by electronic and not by lipophilic properties of the sulfonylureas.[44]

Early-stage leukocyte entrapment in the retinal microcirculation—retinal leukostasis—is considered to be one of the important pathogenetic events in diabetic retinopathy. Since gliclazide was reported to reduce leukocyte adhesion to endothelial cells in hyperglycemia in vitro, selective efficacy of this sulfonylurea in preventing leukostasis was studied in diabetic rats in vivo.[45] A significant reduction in retinal leukostasis was observed in the gliclazide-treated but not in the glibenclamide-treated diabetic group.[45] Thus, gliclazide could directly improve abnormalities in the retinal microcirculation independent of blood glucose control and possibly have selective therapeutic benefits in preventing early, critical events in diabetic retinopathy compared with other sulfonylureas. The Japanese Diabetic Retinopathy Program[46] studied the progression of retinopathy in diabetic patients treated with gliclazide, other sulfonylureas, or placebo. After 5 years, the incidence of preproliferative retinopathy was significantly lower in the group receiving gliclazide compared with those receiving other sulfonylureas despite equivalent metabolic control.[46] The authors concluded that the specific hemobiologic actions of gliclazide appear to offset or delay the progression of diabetic retinopathy and may have the advantage of lowering the incidence of preproliferative retinopathy.

Intensive glycemic control has also been shown to reduce microvascular disease but the effects on macrovascular disease remain uncertain.[1,4] The Action in Diabetes and Vascular disease—PreterAx and DiamicroN MR Controlled Evaluation (ADVANCE) study[47] will examine the hypotheses that lowering blood pressure with an ACE inhibitor–diuretic combination and intensively controlling glycemia with a gliclazide-based regimen in high-risk patients with type 2 diabetes (both hypertensive and nonhypertensive) reduces the incidence of macrovascular and microvascular disease.

In summary, there is an array of evidence that gliclazide MR, in addition to its effect on glycemic control, has independent effects on oxidative stress, lipid peroxidation, monocyte interaction, endothelial function, and platelet fibrin networks that are of vasculoprotective potential.

CONCLUSION

Gliclazide MR, administered once daily, provides efficient glycemic control in the long term with very good acceptability, in particular a low incidence of hypoglycemia in all patients, including the elderly and those patients with mild to moderate renal insufficiency. The efficacy and acceptability of gliclazide MR can be linked to the improvement of insulin secretion toward a physiological profile and to its original binding characteristics with the sulfonylurea receptor. The glycemia-independent effects of gliclazide on some of the key steps of vascular angiopathy may provide vascular protection beyond glycemic control.

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Original article

Hypoglycemia in patients with type 2 diabetes from India and Malaysia treated with sitagliptin or a sulfonylurea during Ramadan: a randomized, pragmatic study

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Abstract

Objective:
To compare the incidence of symptomatic hypoglycemia between sitagliptin and sulfonylurea in Muslim patients with type 2 diabetes who fasted during Ramadan.

Methods:
In a multicenter, pragmatic, randomized study, patients with type 2 diabetes were recruited from clinical centers in India ($n = 765$) and Malaysia ($n = 105$). Eligible patients (age ≥ 18 yrs) expressed their intention to daytime fast during Ramadan, were treated with a stable dose of sulfonylurea with or without metformin for ≥ 3 months prior to screening visit, and had an $HbA_{1c} \leq 10\%$. Patients were randomized in a 1:1 ratio to either switch to sitagliptin 100 mg q.d. or remain on their pre-study sulfonylurea. Daily diary cards were completed to document information on hypoglycemic symptoms and complications. The primary endpoint was the overall incidence of symptomatic hypoglycemia during Ramadan.

Results:
Of the 870 patients randomized, 848 ($n = 421$ for sitagliptin and 427 for sulfonylurea) returned ≥ 1 completed diary card and were included in the analysis. The proportion of patients who recorded ≥ 1 symptomatic hypoglycemic event during Ramadan was lower with sitagliptin (3.8%) compared to sulfonylurea (7.3%). The risk of symptomatic hypoglycemia was significantly lower with sitagliptin (risk ratio [95% CI] = 0.52 [0.29, 0.94]; $p = 0.028$). By country, the proportions of patients who recorded ≥ 1 symptomatic hypoglycemic event during Ramadan were 4.1% vs. 7.7% in India and 1.9% vs. 3.8% in Malaysia for sitagliptin and sulfonylurea, respectively. No patient discontinued treatment due to a hypoglycemic event. One patient on sitagliptin and seven on sulfonylurea had an event that required non-medical assistance. No events required medical assistance. Both treatments were generally well tolerated.

Limitations:
Symptomatic hypoglycemic events did not require a confirmatory blood glucose measurement, which may have overestimated hypoglycemic events. Measures of glycemic control and body weight were not assessed.

Conclusion:
Switching antihyperglycemic treatment to sitagliptin from a sulfonylurea reduced the risk of symptomatic hypoglycemia by approximately 50% for Muslim patients with type 2 diabetes who fasted during Ramadan.

Clinical trial registration:
Clinicaltrials.gov: NCT01340768.

Introduction

During the holy month of Ramadan, Muslims observe a daytime fast and abstain from eating and drinking. Although fasting is the obligatory duty of healthy Muslim adults, the Quran exempts sick people from fasting, including individuals with diabetes[1]. However, the EPIDAR study demonstrated that many diabetic patients fast during Ramadan[2]. Therefore, the American Diabetes Association (ADA) and the Organization of the Islamic Conference have published recommendations for managing diabetes during Ramadan[3,4].

Both the act of fasting and the use of antihyperglycemic therapy may increase the risk of hypoglycemia. This is relevant for diabetic individuals who observe the fast during Ramadan. The EPIDAR study noted a 7.5-fold increase in the incidence of severe hypoglycemia during Ramadan in patients with type 2 diabetes[2]. Furthermore, the incidence of symptomatic hypoglycemia was estimated at 20% during Ramadan in sulfonylurea-treated Muslims with type 2 diabetes[5]. To minimize fasting-related complications during Ramadan, guidelines recommend a pre-Ramadan meeting between patients with diabetes and their physicians to review lifestyle and therapeutic regimens[3].

As many patients with type 2 diabetes are treated with antihyperglycemic agents, guidelines recommend altering the timing of the dose to coincide with the breaking of the fast during Ramadan[3]. Another alternative could be switching therapies with a high risk of hypoglycemia to therapies with a lower risk. Dipeptidyl peptidase-4 (DPP-4) inhibitors are associated with a low risk of hypoglycemia in patients with type 2 diabetes[6]. In a recent study of Muslims from six Middle East countries, patients with type 2 diabetes who had their sulfonylurea treatment switched to the DPP-4 inhibitor sitagliptin had a nearly 50% reduction in risk for symptomatic hypoglycemia compared to those who remained on sulfonylurea during Ramadan[7]. To further evaluate the clinical strategy of switching antihyperglycemic therapy during Ramadan, the present study assessed the incidence of hypoglycemia during Ramadan in sulfonylurea-treated patients from India and Malaysia who were randomly switched to sitagliptin or remained on their pre-study sulfonylurea regimen.

Methods

Patients and study design

Eligible patients were Muslims with type 2 diabetes who were at least 18 years of age, were treated with a stable dose of sulfonylurea (glimepiride, gliclazide [immediate- or modified-release], or glibenclamide) with or without metformin for at least three months, and had an $HbA_{1c} \leq 10\%$ at the screening visit. In addition, patients stated their intention to fast during Ramadan after receiving medical counseling regarding the risks of fasting and provided written informed consent. Patients were excluded if they had type 1 diabetes or gestational diabetes, were pregnant or breast feeding, were treated with antihyperglycemic agents other than a sulfonylurea with or without metformin, had a history of severe hypoglycemia, had hypersensitivity or contraindications to treatment with DPP-4 inhibitors, had serum creatinine $\geq$1.5 mg/dL (males) or $\geq$1.4 mg/dL (females), would have difficulty completing study forms, or were currently participating in another intervention study. Patients were recruited by clinical centers in India and Malaysia. The study was designed in accordance with the principles stated in the Declaration of Helsinki. The protocol was reviewed and approved by the appropriate local authorities, as required, and the institutional review board or ethical review committee for each participating clinical center. The Malaysia study was conducted from 28 June 2010 to 10 October 2010 and the India study was conducted from 27 June 2011 to 21 September 2011. Due to the small sample size in the Malaysian study, a decision was made prior to unblinding the Malaysia study data to combine the data with the India study completed in 2011 for the present analysis.

In this open-label, pragmatic design, eligible patients were randomized in a 1:1 ratio to switch to sitagliptin 100 mg q.d. (with or without metformin) or to remain on their current sulfonylurea treatment (with or without metformin). For allocation to treatment group, each site was provided with a randomization schedule. Randomization was stratified by treatment regimen (monotherapy or in combination with metformin). Following randomization, patients and investigators were not blinded to treatment and the study proceeded under real-life conditions without any additional protocol-mandated intervention. Physicians managed their patients per usual clinical practice and were able to alter drug and/or dose if needed to optimally treat their patients during Ramadan.

At the screening visit, the following information was collected from patient medical records: demographics (age, gender, and ethnicity), diabetic complications, HbA_{1c}, fasting blood glucose, total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, serum creatinine, blood pressure, weight, height, and all medications prior to the start of Ramadan. Patients were provided with daily diary cards to record hypoglycemic symptoms and complications, time from consuming their last meal and time from their last medication dose to the start of the symptoms of hypoglycemia or need for assistance, and whether the fast was observed during the day. If patients experienced symptoms of hypoglycemia, they were instructed to

perform fingerstick glucose measurements and record the results on their diary card. A diary card was to be completed by the patients on a daily basis, regardless of the presence of symptoms. In addition, a preprandial blood glucose measurement was recorded prior to the evening meal three times per week on special color-coded diary cards to identify asymptomatic hypoglycemia (i.e., blood glucose values ≤70 mg/dL). At the follow-up visit at the end of Ramadan (i.e., study end), additional information was collected including confirmation of observance of the fast during Ramadan and changes in diabetes medication dose and dose timing during Ramadan. Safety and tolerability were assessed by reviewing reported adverse events during the study. All adverse events were rated by the study site investigators for intensity and relationship to study drug. Patients were also contacted by phone two weeks after Ramadan to assess the occurrence of any serious adverse events since study end.

Outcome variables

The proportion of patients recording at least one symptomatic hypoglycemic event during Ramadan was the primary endpoint of interest. Symptomatic events of hypoglycemia included any event associated with clinical symptoms such as faintness, headache, confusion, anxiety, sweating, tremor, palpitations, nausea, and pallor. Multiple symptoms experienced by the same patient during any one day were counted as a single event. The secondary endpoint was the proportion of patients with at least one symptomatic or asymptomatic (no reported symptoms but a recorded blood glucose ≤70 mg/dL) hypoglycemic event. Hypoglycemic events were further categorized as events requiring assistance that was either non-medical (e.g., family member or friend) or from medical personnel. Events requiring medical assistance included hypoglycemic events that caused loss of consciousness, seizure, coma, or physical injury or had medical intervention (i.e., visits to doctor's office or emergency room or hospitalization).

Statistics

Baseline demographics and clinical characteristics were summarized by treatment group. The All Patients as Treated (APaT) population was used as the primary analysis population for this study. The APaT population consists of all randomized patients who received at least one dose of study treatment and returned at least one diary card during Ramadan. A supportive analysis using the per-protocol population was also performed. The per-protocol population is a subset of the APaT population, and included only those patients who completed the study on their originally assigned treatment, did not have a major protocol violation, and returned at least 70% of daily diary cards completed. The primary and secondary endpoints were assessed using a stratified Mantel–Haenszel test for the relative risk, with concomitant use of metformin therapy as a stratification factor. For patients who switched therapies after randomization, only the hypoglycemic events that occurred prior to the switch were included in the APaT analysis. The total number of hypoglycemic events in each study arm and types of episodes were also summarized. Assuming an incidence of symptomatic hypoglycemia of 10% in sulfonylurea-treated patients during Ramadan (based on the results of Aravind *et al.*[5]) and that sitagliptin will reduce the risk by 50%, 434 patients per arm were required (two sided $\alpha = 0.05$, with a power of 80%). A p-value < 0.05 (two-sided) was considered statistically significant. All data analyses were performed using SAS (Version 9.1.3, Cary, NC, USA).

Results

Investigators from 25 clinical sites randomized 870 patients, with 436 switched to sitagliptin and 434 remaining on sulfonylurea. Of the randomized patients, 97% completed the study, with slightly more patients discontinuing sitagliptin during the study. The primary reason for discontinuation was loss to follow-up (Figure 1). At study end, 848 (97%) returned at least one diary card and were included in the primary analysis using the APaT population (Figure 1). For the APaT population, baseline characteristics were generally similar between treatment groups (Table 1). Patients from India made up 88% of the APaT population. Overall, 47% were male, mean age was 51 years, and mean HbA_{1c} was 8.0%. In the APaT population ($n = 848$), 63% of all patients were on glimepiride, 24% on glibenclamide, and 13% on gliclazide at the screening visit. Patients had been on sulfonylurea treatment for a median of 1 year and 86% used sulfonylurea in combination with metformin. For those who were randomized to remain on their pre-study sulfonylurea in the APaT population ($n = 427$), 65% were treated with glimepiride, 22% with glibenclamide, and 13% with gliclazide. At baseline, the median dose of sulfonylurea was 2 mg/day for glimepiride, 10 mg/day for glibenclamide, and 80 mg/day for gliclazide in the patients randomized to remain on sulfonylurea. The median dose of metformin was 1000 mg/day and was the same in both treatment groups at baseline.

During Ramadan, the proportion of patients reporting that they did not break the daytime fast for reasons other than to treat the symptoms of hypoglycemia was 98.4% in the sitagliptin group and 97.2% in the sulfonylurea group. The proportion of patients reporting a change in their diabetes medication dose or timing was 13.1% ($n = 55$) in the sitagliptin group and 22.7% ($n = 97$) in the sulfonylurea group, with dose timing accounting for most of the

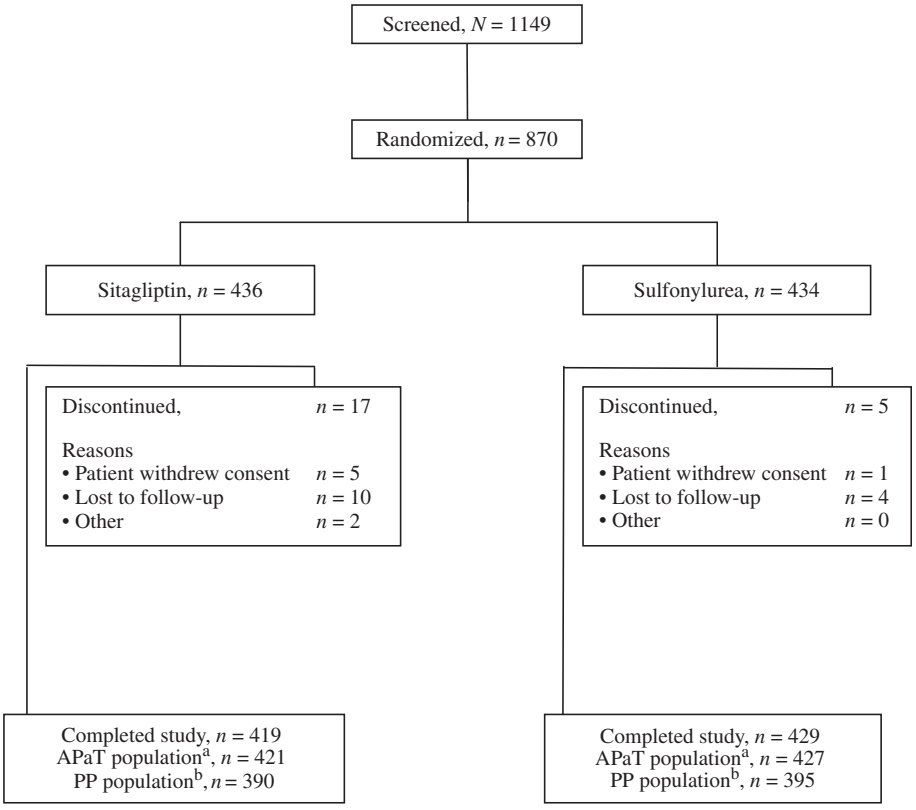

Figure 1. Patient disposition.

[a]The All Patients as Treated (APaT) population consisted of all randomized patients who received at least one dose of study treatment and returned at least one completed diary card during Ramadan. In addition, all patients were analyzed in the treatment groups to which they were randomized, unless they took incorrect study medication for the entire treatment period.

[b]The per-protocol (PP) population was a subset of the APaT population, and included only those patients who completed the study and returned at least 70% of their diary cards completed.

changes. The median dose of sulfonylurea or metformin was identical between baseline and study end in the patients randomized to remain of sulfonylurea during Ramadan. Four patients in the sitagliptin group had their antihyperglycemic therapy changed to a sulfonylurea during follow-up, while no patients in the sulfonylurea group changed therapy.

In the APaT cohort, a lower proportion of sitagliptin-treated patients reported at least one symptomatic hypoglycemic event during Ramadan compared to those treated with a sulfonylurea (3.8% vs. 7.3%; Table 2). The risk of symptomatic hypoglycemia was significantly lower with sitagliptin relative to sulfonylurea treatment (Mantel–Haenszel relative risk ratio [95% CI] = 0.52 [0.29, 0.94]; $p = 0.028$). Overall, 85 symptomatic hypoglycemic events were reported during Ramadan by patients in the APaT cohort, with 22 events in 16 patients in the sitagliptin group and 63 events in 31 patients in the sulfonylurea group. The number of patients reporting at least two symptomatic hypoglycemic events was three in the sitagliptin group and nine in the sulfonylurea group. No hypoglycemic event resulted in discontinuation of study drug.

The proportion of patients with symptomatic hypoglycemia confirmed with a corresponding blood glucose value ≤70 mg/dL was 2.1% ($n/n = 9/421$) in the sitagliptin group and 5.4% (23/427) in the sulfonylurea group. One patient (0.2%) in the sitagliptin group and two (0.5%) in the sulfonylurea group reported a symptomatic hypoglycemic event that had a corresponding blood glucose value <50 mg/dL. Among the patients randomized to remain on sulfonylurea treatment, the proportion of patients reporting at least one symptomatic hypoglycemic event was 9.1% ($n/n = 25/276$) in the glimepiride, 5.2% (5/96) in the glibenclamide, and 1.8% (1/55) in the gliclazide subgroups. Although a lower proportion of Malaysian patients reported symptomatic hypoglycemia compared to those from India, the relative between-treatment trend was similar between countries (Table 2).

The total proportion of symptomatic or asymptomatic hypoglycemic events was 4.8% in the sitagliptin group and 9.6% in the sulfonylurea group (Table 3). The risk of symptomatic or asymptomatic hypoglycemia was significantly lower with sitagliptin relative to sulfonylurea treatment (Mantel–Haenszel relative risk ratio [95% CI] = 0.49

Table 1. Baseline characteristics of randomized patients who completed at least one daily diary card during Ramadan (APaT population).

	Sitagliptin ($n=421$)	Sulfonylurea ($n=427$)
Patients by country		
India, *n* (%)	368 (87)	375 (88)
Malaysia, *n* (%)	53 (13)	52 (12)
Characteristics		
Age at baseline, years	51.4 ± 9.9	50.7 ± 10.0
(min, max)	(26, 80)	(23, 78)
Male, *n* (%)	208 (49)	194 (45)
Body mass index, kg/m^2	27.4 ± 6.0	27.5 ± 4.7
HbA_{1c}, %	8.0 ± 1.1	7.9 ± 1.2
Fasting blood glucose, mg/dL	150 ± 60	147 ± 46
Duration of diabetes, years*	3.0	3.0
Concomitant metformin therapy, *n* (%)	357 (85)	368 (86)
Systolic blood pressure, mmHg	129 ± 13	129 ± 14
Diastolic blood pressure, mmHg	81 ± 8	80 ± 8
Total cholesterol, mg/dL	187 ± 40	180 ± 38
LDL cholesterol, mg/dL	110 ± 35	106 ± 33
HDL cholesterol, mg/dL	43 ± 10	43 ± 12
Triglycerides, mg/dL*	149	142
Serum creatinine, mg/dL	0.94 ± 0.21	0.96 ± 0.48
Diabetes- and cardiovascular-related complications and comorbidities		
Neuropathy, *n* (%)	27 (6)	28 (7)
Retinopathy, *n* (%)	9 (2)	8 (2)
Nephropathy, *n* (%)	4 (1)	6 (1)
Coronary artery disease, *n* (%)	5 (1)	14 (3)
Peripheral arterial disease, *n* (%)	0 (0.0)	0 (0.0)
Cerebrovascular disease, *n* (%)	2 (1)	2 (1)
Hypertension	161 (38)	173 (41)
Dyslipidemia	135 (32)	141 (33)

Data are expressed as proportion, *n* (%), or mean ± standard deviation unless otherwise indicated.
*Median.

Table 2. Incidence of symptomatic hypoglycemia during Ramadan (APaT population).

n/*n* (%) of patients experiencing events	Sitagliptin	Sulfonylurea	Risk ratio (95% CI)
Overall	16/421 (3.8)	31/427 (7.3)	0.52 (0.29, 0.94)*
India	15/368 (4.1)	29/375 (7.7)	–
Malaysia	1/53 (1.9)	2/52 (3.8)	–

n/*n* = number of patients with at least one episode of symptomatic hypoglycemia/number of patients in the specific group.
– = not calculated.
*$p=0.028$.

[0.29, 0.83]; $p=0.006$). The proportion of patients reporting a hypoglycemic event that required non-medical assistance was low (0.2% in the sitagliptin group and 1.6% in the sulfonylurea group). There were no reported events that required medical assistance during Ramadan (Table 3).

Of the 870 patients randomized to treatment, 90% ($n=785$) met the per-protocol criteria (i.e., randomized patients who completed the study and returned at least 70% of their diary cards completed) (Figure 1). In the per-protocol population, 3.6% ($n/n=14/390$) of patients in the sitagliptin group and 7.8% ($n/n=31/395$) in the sulfonylurea group reported at least one symptomatic hypoglycemic event. In this cohort, the risk of symptomatic hypoglycemia was significantly lower with sitagliptin relative to sulfonylurea treatment (Mantel–Haenszel relative risk ratio [95% CI] = 0.45 [0.24, 0.84]; $p=0.010$).

The proportion of patients reporting an adverse event other than hypoglycemia was slightly higher in the sitagliptin group (10.0%) compared to the sulfonylurea group (7.0%) (Table 4). The proportion of patients with adverse events considered by the investigator to be related to study drug was similar between groups. One serious adverse event (automobile accident) was reported in the sitagliptin group and resulted in discontinuation of study drug. No serious adverse events were reported in the sulfonylurea group. No deaths were reported. Three adverse events (blood glucose decreased, hyperglycemia, and pyrexia) occurred in at least 1% of patients, with small differences between groups (Table 4). No patients in the sulfonylurea group and five patients in the sitagliptin discontinued treatment due to an adverse event. Of the events leading to discontinuation, three patients had events that were considered to be related to study drug (gastritis, hyperchlorhydria/hyperacidity, and hyperglycemia).

Discussion

Hypoglycemia is a well known risk associated with the daytime fasting required during Ramadan, especially for individuals with type 2 diabetes[2]. Treatment guidelines recommend strategies to manage patients and their diabetes during Ramadan[3]. The present study investigated a potential strategy to reduce the risk of symptomatic hypoglycemia during Ramadan in sulfonylurea-treated patients with type 2 diabetes from India and Malaysia. Patients were randomized to either switch their pre-study sulfonylurea to sitagliptin or to remain on their pre-study sulfonylurea, with or without metformin, during Ramadan. Treatment with sitagliptin was associated with a 48% relative reduction in risk of symptomatic hypoglycemia during Ramadan compared to sulfonylurea treatment. The total number of symptomatic hypoglycemic events was also lower in the sitagliptin group compared to that in the sulfonylurea group, with three patients reporting at least two symptomatic hypoglycemic events in the sitagliptin group compared to nine patients in the sulfonylurea group. A sensitivity analysis using the per-protocol population yielded a similar relative reduction in risk (55%) with sitagliptin. The lower incidence of hypoglycemia with sitagliptin was observed in both countries. No events of hypoglycemia required medical assistance and both treatments were generally well tolerated

Table 3. Proportion of patients reporting hypoglycemia during Ramadan by type of event (APaT population).

n (%) of patients experiencing:	Sitagliptin (*n* = 421)	Sulfonylurea (*n* = 427)	Risk ratio (95% CI)
Symptomatic or asymptomatic hypoglycemic events	20 (4.8)	41 (9.6)	0.49 (0.29, 0.83)*
Any hypoglycemic events requiring non-medical assistance	1 (0.2)	7 (1.6)	–
Any hypoglycemic events requiring medical assistance	0	0	–

Types of hypoglycemic event defined in Methods.
– = not calculated.
*$p = 0.006$.

Table 4. Summary of clinical adverse events (AEs) other than hypoglycemia (APaT population).

	Sitagliptin *n* = 421 *n* (%)	Sulfonylurea *n* = 427 *n* (%)
With one or more AEs	42 (10.0)	30 (7.0)
With drug-related AEs†	9 (2.1)	7 (1.6)
With serious AEs	1 (0.2)	0 (0.0)
With serious drug-related AEs†	0 (0.0)	0 (0.0)
Who died	0 (0.0)	0 (0.0)
Discontinued due to an AE	5 (1.2)	0 (0.0)
Discontinued due to a drug-related AE†	3 (0.7)	0 (0.0)
Discontinued due to a serious AE	1 (0.2)	0 (0.0)
Discontinued due to a serious drug-related AE†	0 (0.0)	0 (0.0)
AEs with an incidence ≥1% in either group		
Blood glucose decreased	1 (0.6)	6 (1.4)
Hyperglycemia	11 (2.6)	7 (1.6)
Pyrexia	5 (1.2)	6 (1.4)

†Determined by the investigator to be related to the drug.

during Ramadan. The present findings confirm those from a similarly designed study in 1066 Muslims with type 2 diabetes from six Middle East countries[7]. In that study, the incidence of symptomatic hypoglycemia was 6.7% in the sitagliptin group and 13.2% in the sulfonylurea group, and the resultant relative decrease in risk was nearly 50%. Collectively these results confirm that switching antihyperglycemic therapy with a high risk of hypoglycemia to one with a lower risk is an appropriate therapeutic approach for disease management. Furthermore, this strategy could be used for other religious or cultural events that require extended alterations in meal patterns such as fasting or meal skipping.

Previous studies have compared another DPP-4 inhibitor and sulfonylurea in patients with type 2 diabetes during Ramadan. In an open-label, prospective study in India, 97 Muslim patients were randomly assigned to treatment with the DPP-4 inhibitor vildagliptin or a sulfonylurea, with or without metformin, during Ramadan. The proportion of patients reporting hypoglycemia was numerically lower with DPP-4 inhibitor vildagliptin (0%), compared to sulfonylurea (4.8%)[8]. Small UK observational studies reported a lower incidence of hypoglycemia with vildagliptin compared to gliclazide during Ramadan[9,10]. It is difficult to compare results across the sitagliptin and vildagliptin trials because of the different study designs, sample sizes, treatment regimens and assignments, and definitions of hypoglycemia, but the differences in hypoglycemic risk is likely attributable to the differences in the mechanisms of action between DPP-4 inhibitors and sulfonylureas[11,12].

Sulfonylurea use is associated with an increased risk of hypoglycemia[13]. In a five-country, observational study, the overall incidence of symptomatic hypoglycemia was 20% in nearly 1,400 type 2 diabetic patients treated with a sulfonylurea during Ramadan, with 13% of the 396 patients from India and 24% of the 356 patients from Malaysia reporting hypoglycemia[5]. In the present study, the proportion of sulfonylurea-treated patients reporting at least one symptomatic hypoglycemic event was 7.3% overall (7.7% in Indian patients and 3.8% in Malaysian patients). The difference in the incidence of hypoglycemia in sulfonylurea-treated patients reported in the present study and in the aforementioned observational study may be related to different study designs (randomized vs. observational), greater patient–physician interaction in the present study, and potentially different study populations and dietary habits. In a cohort of patients with type 2 diabetes mainly treated with a sulfonylurea-based regimen, Bravis *et al.*[14] reported a 58% reduction in risk of

hypoglycemia during Ramadan in patients randomized to receive Ramadan-focused education from their physician compared to those not receiving any education.

The present study was not adequately powered to compare the incidence of hypoglycemia for each type of sulfonylurea relative to sitagliptin. There were, however, notable differences in sample sizes and reported hypoglycemic events across the sulfonylureas. A majority of patients were treated with glimepiride (65%) relative to glibenclamide (22%) and gliclazide (13%) during Ramadan. Patients treated with glimepiride or glibenclamide reported a higher incidence of symptomatic hypoglycemia compared with sitagliptin-treated patients. The incidence of hypoglycemia was low and similar between sitagliptin and gliclazide in the present study. These findings are generally consistent with those recently reported for sitagliptin and sulfonylurea treatments in the Middle East Ramadan study[7]. Previously, we observed that patients treated with gliclazide had a lower incidence of hypoglycemia during Ramadan relative to other sulfonylureas[5]. Collectively, these results suggest that sulfonylurea selection during Ramadan influences the risk of hypoglycemia.

The following strengths and limitations need to be considered for this study. The study used a randomized, pragmatic design with a large sample size. Of the 870 randomized patients, greater than 97% completed the study and were included in the primary analysis. A sensitivity analysis focused on those in the per-protocol population confirmed the overall findings. Furthermore, a similarly designed clinical trial in a different patient population showed comparable results[7]. Daily diary cards were used to capture the occurrence of hypoglycemic symptoms, if present, rather than recalling such symptoms at study end. However, the study was unblinded following randomization and physicians and patients may have changed their behavior based on the randomized treatment assignment, given the objective of the study was to evaluate the incidence of hypoglycemia. Blood glucose measurements were not required to confirm the hypoglycemic episodes as assessed by the primary endpoint (symptomatic hypoglycemic events). The lack of a confirmatory glucose measurement may have overestimated the incidence of hypoglycemia. Alternatively, hypoglycemia may also have been underestimated due to hypoglycemia unawareness in patients with more advanced disease states. Treatment efficacy was not evaluated and may have contributed to the variation in hypoglycemic episodes between groups in the present study.

Conclusion

In conclusion, switching antihyperglycemic treatment to sitagliptin from a sulfonylurea reduced the risk of symptomatic hypoglycemia by approximately 50% for Muslim patients with type 2 diabetes who fasted during Ramadan. Thus, switching antihyperglycemic therapy is an appropriate therapeutic option for physicians to consider for the management of their patients with type 2 diabetes who choose to observe the daytime fast during Ramadan.

Transparency

Declaration of funding

The study was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co. Inc., Whitehouse Station, NJ, USA – the manufacturer of sitagliptin.

Declaration of financial/other interests

S.R.A. reported receiving grant money for his institution from MSD (Merck Sharp & Dohme Corp.), receiving consultancy fees/honoraria from MSD, travel support for an investigator meeting related to this study, and receiving payments from other pharmaceutical companies for lectures and speaker bureaus and development of education presentations. S.B.I. reported receiving grant money for his institution from MSD and receiving consultancy fees/honoraria from MSD. R.B. reported receiving grant money for his institution from MSD. J.B.G. has disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article. T.Wa., S.M.L., S.S., M.J.D., C.J.G., H.L.K., L.R., S.S.E., and T.Wo. are employees of Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA and may own company stock or stock options.

CMRO peer reviewers have received honoraria for their review work on this manuscript, and have disclosed that they have no other relevant financial relationships.

Author Contributions: S.S., C.J.G., H.L.K., S.S.E., and L.R. were involved in the concept and design of the study. S.R.A., S.B.I., R.B., J.B.G., T.Wa., S.M.L., S.S., and T.Wo. were involved in the data collection and/or analysis. All authors were involved in interpretation of the results. M.J.D. drafted the article and all authors were involved in the critical revision and approval of the article.

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Review

Diabetes, Hypertension, and Cardiovascular Disease: Clinical Insights and Vascular Mechanisms

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ABSTRACT

Hypertension and type 2 diabetes are common comorbidities. Hypertension is twice as frequent in patients with diabetes compared with those who do not have diabetes. Moreover, patients with hypertension often exhibit insulin resistance and are at greater risk of diabetes developing than are normotensive individuals. The major cause of morbidity and mortality in diabetes is cardiovascular disease, which is exacerbated by hypertension. Accordingly, diabetes and hypertension are closely interlinked because of similar risk factors, such as endothelial dysfunction, vascular inflammation, arterial remodelling, atherosclerosis, dyslipidemia, and obesity. There is also substantial overlap in the cardiovascular complications of diabetes and hypertension related primarily to microvascular and macrovascular disease. Common mechanisms, such as upregulation of the renin-angiotensin-aldosterone system, oxidative stress, inflammation, and activation of the immune system likely contribute to the close relationship between diabetes and hypertension. In this article we discuss diabetes and hypertension as comorbidities and discuss the pathophysiological features of vascular complications associated with these conditions. We also highlight some vascular mechanisms that predispose to both conditions, focusing on advanced glycation end products, oxidative stress, inflammation, the immune system, and microRNAs. Finally, we provide some insights into current therapies targeting diabetes and cardiovascular complications and introduce some new agents that may have vasoprotective therapeutic potential in diabetes.

RÉSUMÉ

L'hypertension et le diabète de type 2 sont des affections concomitantes fréquentes. L'hypertension est deux fois plus fréquente chez les patients atteints de diabète que chez ceux qui n'en sont pas atteints. De plus, les patients atteints d'hypertension sont souvent résistants à l'insuline et sont plus susceptibles de souffrir de diabète que les personnes normotendues. Chez les diabétiques, la principale cause de morbidité et de mortalité est la maladie cardiovasculaire, qui est exacerbée par l'hypertension. En conséquence, le diabète et l'hypertension sont étroitement interreliés en raison de facteurs de risques similaires, comme la dysfonction endothéliale, l'inflammation vasculaire, le remodelage artériel, l'athérosclérose, la dyslipidémie et l'obésité. On observe un chevauchement important entre les complications cardiovasculaires du diabète et celles de l'hypertension liées principalement à des maladies microvasculaires et macrovasculaires. Des mécanismes communs, comme une stimulation du système rénine-angiotensine-aldostérone, un stress oxydatif, une inflammation et une activation du système immunitaire, sont susceptibles de contribuer à la relation étroite entre le diabète et l'hypertension. Dans cet article, nous abordons le diabète et l'hypertension comme des affections concomitantes et nous parlons des caractéristiques physiopathologiques des complications vasculaires associées à ces affections. Nous soulignons également certains mécanismes vasculaires qui prédisposent à ces deux affections, en mettant l'accent sur les produits finaux de glycation avancée, le stress oxydatif, l'inflammation, le système immunitaire et les micro-ARN. Finalement, nous présentons certaines connaissances sur les traitements actuels ciblant le diabète et les complications cardiovasculaires et nous présentons de nouveaux agents qui pourraient avoir un pouvoir vasoprotecteur chez les patients diabétiques.

Type 2 Diabetes Mellitus and Hypertension

The prevalence of obesity and type 2 diabetes (T2D) continues to rise worldwide as lifestyles associated with low energy expenditure and high caloric intake are increasingly adopted, particularly in lower-income and developing countries. It is predicted that the number of cases of T2D will rise from 415 million to 642 million by 2040.[1] Hypertension is even more common, rising in prevalence in the same countries, with a recent worldwide estimate of 1.39 billion cases.[2]

Although T2D and hypertension can be simply diagnosed at the bedside, they are each complex and heterogeneous phenotypes associated with an elevated risk of life-threatening cardiovascular disease (CVD). Their frequent coexistence in the same individual is not a coincidence, because aspects of the pathophysiology are shared by both conditions, particularly those related to obesity and insulin resistance. For

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example, in the San Antonio Heart Study, 85% of those with T2D had hypertension by the fifth decade of life, whereas 50% of those with hypertension experienced impaired glucose tolerance or T2D.[3]

In health, insulin maintains glucose homeostasis by integrated actions on carbohydrate, protein, and lipid metabolism. Loss of sensitivity to aspects of insulin action (insulin resistance) principally affects the liver, muscle, and adipose tissues and is selective for glucose and lipid metabolism, eg, sparing insulin's action to retain sodium in the distal tubule.[4,5] Reduction in insulin-mediated glucose disposal leads to compensatory hypersecretion of insulin to maintain homeostasis: Glucose intolerance ensues if this endocrine pancreas response is inadequate, although some obese individuals avoid T2D by virtue of a supranormal B-cell response.[6] Recently, the role of adipose tissue in these associations has been increasingly appreciated.[7]

Diabetes is associated with both macrovascular (involving large arteries such as conduit vessels) and microvascular (involving small arteries and capillaries) disease. Chronic hyperglycemia and insulin resistance play an important role in the initiation of vascular complications of diabetes and involve a number of mechanisms including (1) increased formation of advanced glycation end products (AGEs) and activation of the receptor for advanced glycation end products (RAGE) AGE-RAGE axis, (2) oxidative stress, and (3) inflammation.[8] In addition, emerging evidence suggests a role for microRNAs (miRNAs) in the vasculopathy of diabetes (see further on).[9] Hypertension is an important risk factor for diabetes-associated vascular complications, because hypertension itself is characterized by vascular dysfunction and injury (Fig. 1).

In this review, we focus on vascular complications of diabetes and discuss the impact of comorbidities, specifically hypertension. The role of oxidative stress and inflammation as "common soil" for metabolic and vascular disease are highlighted. We also discuss how some of the newer agents used in the treatment of T2D can influence blood pressure (BP) regulation and the risk of CVD, with an eye to future developments more specifically targeting vascular protection.

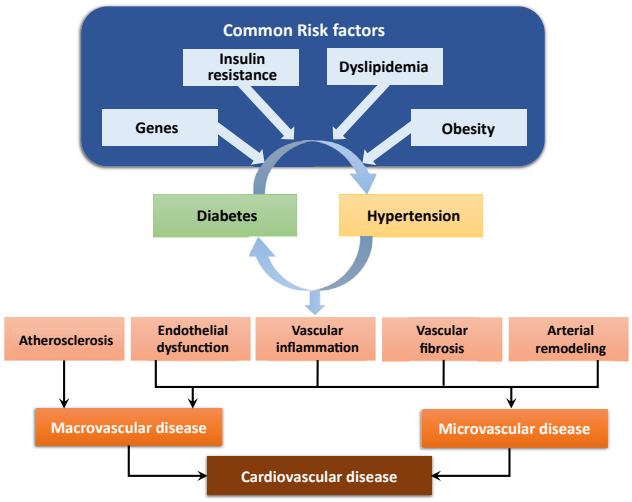

Figure 1. Vascular processes whereby diabetes and hypertension predispose to cardiovascular disease. Common risk factors promote diabetes and hypertension, which are associated with atherosclerosis, vascular inflammation, endothelial dysfunction, and structural remodelling, which lead to macrovascular and microvascular disease. Vascular damage and endothelial dysfunction is amplified when diabetes and hypertension coexist.

Macrovascular Disease

Clinical features

Macrovascular (or cardiovascular) disease of larger conduit arteries is a complex inflammatory process leading to myocardial infarction, stroke, and peripheral artery disease. The primary pathologic process associated with macrovascular disease is atherosclerosis, which in diabetes is accelerated with extensive distribution of vascular lesions.[10] T2D confers an approximate 2-fold elevation in CVD risk, equivalent to that of a previous myocardial infarction.[11,12] Moreover, patients with T2D have poorer outcomes after an acute coronary syndrome and higher rates of reinfarction and heart failure.[13]

Elevation of CVD risk begins at the stage of prediabetes in association with insulin resistance and impaired glucose tolerance.[14] As well as being the diagnostic hallmark of T2D, hyperglycemia is the principal determinant of microvascular complications of T2D and plays an important role in the pathogenesis of CVD. However, in established T2D, it is a relatively weak modifiable risk factor compared with hypertension, dyslipidemia, and (unfortunately in many populations) cigarette smoking.[15,16]

Pathophysiological features

Insulin resistance is detectable for several years before the onset of T2D. It is associated with obesity, particularly central obesity, but may be present in lean individuals with hypertension.[17] During calorie excess, adipocytes in obese humans—whether in subcutaneous or visceral areas—undergo hypertrophy. Visceral adipocytes are more susceptible to cellular death as they begin to enlarge and their stromal vascular fraction becomes infiltrated with macrophages.[18]

These macrophages around dead adipocytes form "crown-like structures," a histologic appearance that is associated with expression of cytokines (including tumor necrosis factor-α [TNF-α], interleukin-6 [IL-6]), and inducible nitric oxide synthase.[19] These changes have been shown to coincide with the onset of insulin resistance and provide a pathophysiological link between metabolic and vascular disease.[20]

In addition to these proinflammatory changes, adipocyte hypertrophy is associated with larger triglyceride stores, a higher lipolytic rate, and an atherogenic lipid profile: elevated concentrations of small dense low-density lipoprotein cholesterol, high concentrations of triglycerides, triglyceride-rich remnants, very low-density lipoprotein cholesterol, and apolipoprotein B, usually in combination with low levels of high-density lipoprotein cholesterol.[7] This profile is associated with increased production of leptin, decreased production of adiponectin, higher circulating levels of nonesterified fatty acids (NEFAs), and activation of mitochondrial oxidative stress pathways in vascular endothelial cells.[7]

These proinflammatory and metabolic consequences of obesity and insulin resistance result in endothelial

dysfunction, a key antecedent and modulator of atherosclerosis that has been demonstrated not only in hypertension but also in prediabetes,[21] first-degree relatives of individuals with T2D,[22] and even insulin-resistant healthy individuals.[22,23] It is characterized by disruption of the intricate physiological balance between vasoconstrictors (endothelin, angiotensin II) and vasodilators (nitric oxide, prostacyclin), growth promoting and inhibitory factors, proatherogenic and antiatherogenic factors, and procoagulant and anticoagulant factors.[24,25] A substantial body of evidence suggests that impaired endothelium-dependent vasodilation may in turn contribute to or exacerbate insulin resistance by limiting the delivery of substrate (glucose) to key target tissues.[26]

In addition to these functional changes, an associated low-grade inflammation in endothelial and smooth muscle cells of the vascular wall causes cell proliferation, hypertrophy, remodelling, and apoptosis.[27] This accelerates disruption of the balance between the arterial wall scaffolding proteins elastin and collagen that determine vascular compliance, a form of "vascular aging," which is a characteristic phenotype in hypertension.[28-31] Vascular stiffening leads to widening of arterial pulse pressure and increased pulsatile shear, exacerbating endothelial dysfunction and vascular disease.[32]

Microvascular Disease

Clinical features

Microvascular disease leads to retinopathy, nephropathy, and neuropathy, which are major causes of morbidity and mortality in patients with diabetes. In the United States, diabetic retinopathy affects about 28% of individuals with established T2D.[33] Worldwide it is responsible for 10,000 cases of blindness every year.[34,35] Diabetic nephropathy affects about 25% of individuals with T2D and is the most common cause of renal failure in the United States.[36] Neuropathy affects about 20% of these individuals, although it is estimated that about 50% have neuropathy at some point in their lives.[36] Each of these organ-specific microvascular complications has its own unique clinical and histologic features, but all are common with increasing duration of hyperglycemia and are driven by its downstream cellular effects, including polyol accumulation (resulting from saturation of the hexokinase pathway and consequent increased activity of aldose reductase), AGE-induced injury, increased vascular permeability, and oxidative stress.[8]

Follow-up of the **A**ction in **D**iabetes and **Va**scular Disease: Preterax and Diamicro**n** **C**ontrolled **E**valuation (ADVANCE) trial cohort has confirmed that the presence of microvascular complications increases the risk of cardiovascular complications in individuls with T2D.[37] Moreover, the coexistence of hypertension and retinopathy is a risk factor for the progression of nephropathy. There is evidence that treatment of hypertension with angiotensin II receptor blockers can reduce the progression of retinopathy in addition to well-known effects on nephropathy.[38]

Pathophysiological features

Pathognomonic alterations of diabetic microangiopathy include capillary basement membrane thickening, increased endothelial permeability, and endothelial and vascular smooth muscle cell dysfunction. Hyperglycemia is the key stimulus for these processes by stimulating vasoinjurious signalling pathways, activating the polyol pathway, increasing oxidative stress, stimulating proinflammatory transcription factors, and activation of immune responses. Similar processes are induced by hypertension.[39]

Mechanisms of Vascular Complications in Diabetes and the Impact of Hypertension

A number of interacting mechanisms are in play as summarized in the following sections (Fig. 2).

AGE-RAGE axis

AGEs are compounds that have undergone irreversible posttranslational modifications because of reactions between sugars and amino groups on proteins and nucleic acids. Hyperglycemia accelerates formation of AGEs, which accumulate in the extracellular matrix of vessels and contribute to vascular damage in diabetes.[40] AGEs stimulate production of reactive oxygen species (ROS), which in turn further enhance AGE formation. AGEs are also antigenic and hence induce immune responses.[40] In addition to AGEs, dicarbonyl methylglyoxal, a by-product of glycolysis, accumulates in tissues and contributes to diabetes-associated vascular damage.[41]

AGEs interact with 2 main types of cell surface receptors: (1) scavenger receptors, which remove and degrade AGEs, and (2) receptors for AGEs (RAGE), which trigger specific cellular signalling responses on AGE binding. RAGE is a member of the immunoglobulin family and binds many ligands besides AGEs, such as high mobility group protein B1, S100 calcium-binding proteins (including calgranulin), amyloid-β-protein, and amphotericin. AGE-RAGE signals through transforming growth factor (TGF)-β, NF-κB, mitogen-activated protein kinases (MAPK; ERK1/2, p38MAPK), and nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (Nox) and induces expression of vascular adhesion molecule 1, E-selectin, vascular endothelial growth factor, and proinflammatory cytokines (IL-1β, IL-6, TNF-α).[42] In diabetes, activation of these signalling pathways is increased in vascular smooth muscle cells, leading to vascular fibrosis, calcification, inflammation, prothrombotic effects, and vascular damage, processes underlying diabetic nephropathy, retinopathy, neuropathy, and atherosclerotic CVD.[43] Coexisting hypertension amplifies these complications and contributes to the

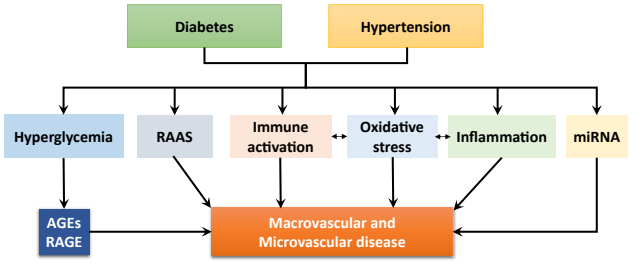

Figure 2. Putative mechanisms whereby diabetes and hypertension cause vascular disease. Immune cell activation and inflammation are mediated through oxidative stress. AGEs, advanced glycation end products; RAAS, renin-angiotensin-aldosterone system; RAGE, receptor AGE.

accelerated vasculopathy in diabetes.[44] Patients with diabetes have increased tissue and circulating concentrations of AGEs and soluble RAGE, which is predictive of cardiovascular events and all-cause mortality. As such, urinary and plasma AGE levels and soluble RAGE may act as biomarkers for vascular disease in diabetes.[45]

Targeting AGE-RAGE has been considered a potential therapeutic strategy to reduce or prevent CVD in diabetes. A number of large clinical trials investigating cardiovascular benefits of alagebrium (ALT-711), which reduces accumulation of AGEs by cleaving AGE cross-links, have been undertaken. They include Distensibility Improvement and Remodeling in Diastolic Heart Failure (DIAMOND; NCT00043836), Systolic and Pulse Pressure Hemodynamic Improvement By Restoring Elasticity (SAPPHIRE; NCT00045981), **S**ystolic Hypertension **I**nteraction With **L**eft **Ve**ntricular **R**emodeling (SILVER; NCT00045994), **S**ystolic **P**ressure **Effica**cy and Safety **Tri**al of **A**lagebrium (SPECTRA; NCT00089713), **B**eginning a **R**andomized **E**valuation of the **A**GE Brea**k**er Alagebrium in **D**iastolic **H**eart **F**ailure I (BREAK-DHF-I; NCT00662116), and Evaluating the Efficacy and Safety of Alagebrium (ALT-711) in Patients With Chronic Heart Failure (BENEFICIAL; NCT00516646). However few data have been published from these studies. Some small clinical studies demonstrated cardiovascular benefit in patients with diabetes and hypertension.[46] In particular, alagebrium improved endothelial function, reduced aortic stiffness, and increased vascular compliance.[47]

Oxidative stress and Nox

Oxidative stress is a key mechanism of glucotoxicity in diabetes, as evidenced by increased vascular ROS generation in response to hyperglycemia and accumulation of oxidation by-products of lipids, proteins, and nucleic acids.[27] NADPH oxidases and dysfunctional endothelial nitric oxide synthase are principal sources of increased ROS in human vasculature in T2D.[48,49] ROS interact with DNA and stimulate many redox-sensitive signalling pathways that lead to inflammation, fibrosis, and vascular damage. Increased vascular oxidative stress in diabetes and hypertension promotes posttranslational oxidative modification of proteins, causing cellular damage and vascular dysfunction. Hyperglycemia also induces activation of redox-sensitive protein kinase C and polyol and hexosamine pathways, further contributing to mitochondrial dysfunction, oxidative stress, endoplasmic reticulum stress, and consequent cellular damage.[50] Oxidative stress is also associated with reduced bioavailability of the vasodilator nitric oxide, causing endothelial dysfunction.

Diabetes-induced oxidative stress is caused by numerous processes, including glucose-stimulated mitochondrial respiration, endoplasmic reticulum stress, activation of the renin-angiotensin system (which is pro-oxidant), decreased vascular antioxidant capacity, reduced activity of the master antioxidant transcription factor nuclear factor-erythroid 2-related factor (Nrf-2), and activation of Nox isoforms.[51] Of these mechanisms activation of Nox types is particularly important. Four Nox isoforms have been demonstrated in human vessels, including Nox1, Nox2, Nox4, and Nox5. Nox-derived ROS influence redox-sensitive signalling pathways in vascular cells such as MAPKs, protein tyrosine phosphatases, transcription factors, Ca^{2+} channels, ion transporters, and proinflammatory genes.[52] In diabetes and hypertension, oxidative stress (increased ROS bioavailability) promotes vascular inflammation, fibrosis, and injury, processes that are normalized by Nox inhibitors or ROS scavengers, or both. Nox1, but not Nox4, seems to be important in atherosclerosis in diabetes, as we demonstrated in Nox1-deficient mice on the atherosclerosis-prone $ApoE^{-/-}$ background made diabetic with streptozotocin.[53] Nox4 has been implicated in renal injury in mouse models of diabetes, effects that are ameliorated with Nox1/4 inhibitors and in mice deficient in Nox4.[54,55] Nox5 may also be important in diabetes-associated vascular injury and nephropathy. We demonstrated that renal Nox5 expression is increased in patients with diabetic nephropathy. Moreover, in transgenic mice with podocyte-specific expression of human Nox5, renal injury was amplified by diabetes.[56] Similar findings were observed in mice expressing human Nox5 in a vascular smooth muscle cell-specific manner.[57] Although extensive experimental evidence showed a renoprotective effect of Nox4 inhibition in diabetes, a recent clinical study using GKT137831, a Nox1/4 inhibitor, failed to show improvement in renal function in patients with diabetic nephropathy.[58] Whether targeting Nox5 may have better clinical outcomes is unclear, because to date there are no Nox5 inhibitors available.

Inflammation and the immune system

Links between inflammation and the immune system with metabolic dysfunction, hypertension, and cardiovascular morbidity are supported by extensive experimental data.[59] This encompasses a number of immune metabolic aspects, including the key role of the tricarboxylic cycle or sphingosine-1-phosphate in the regulation of vascular inflammation.[59,60] Clinical studies have shown that patients with T2D have increased total leukocyte counts, particularly neutrophils and lymphocytes, that correlate with insulin sensitivity,[61] which is in part mediated by inflammatory changes of adipose tissue.[62] Inflammatory biomarkers are also useful in developing targeted cardiovascular therapies in the context of metabolic dysfunction.[63] The link between inflammation and T2D is further supported by genetic studies and clinical trials showing protective effects of immune-targeted therapies and anti-inflammatory actions of classic antidiabetes drugs.[64] Circulating and locally produced effector cytokines such as TNF-α, interferon-γ, IL-1β, and IL-12 may influence insulin sensitivity of peripheral tissues and can modulate insulin release in the pancreatic islets.[65-68] Increased glucotoxicity and lipotoxicity have been associated with immune cell infiltration of target tissues, thereby affecting diabetes-associated target organ damage and cardiovascular complications,[68,69] including the development of metabolic cardiomyopathy.[70,71] Inflammation is a key modulator of metabolic and diabetic CVD.

Genetic evidence. Although genome-wide association studies (GWAS) for insulin resistance or T2D have not shown strong associations with immune-related genes, numerous metabolic traits are linked to immune-related loci.[72] Studies integrating metabochip approaches with GWAS have shown

that classic immunometabolic genes including JNK signalling pathways (such as *MAP3K1*), nuclear factor kappa B (NF-κB) regulators (*MACROD1*), inflammasome activators (NRF3), and interferon-γ receptor genes associate with T2D.[73,74] This also corresponds to results of recent large T2D GWAS that identified genes related to macrophage function and antigen presentation (*MAEA*, *ST6GAL1*), and T-cell signalling (*CMIP* or *PTPRJ*).[72,75] While trying to interpret these important studies, it should be appreciated that GWAS approaches have limitations, because only a small component of heritability of complex traits is directly explainable by single-gene variability.[76]

Clinical evidence. Increasing clinical evidence indicates an immune component in T2D and its cardiovascular complications. Immune-targeted therapies currently available for the treatment of rheumatoid arthritis and autoimmune disorders, including anti-TNF therapies, may prevent insulin resistance as well as cardiovascular risk.[64,77] A recent meta-analysis of studies with anti-TNF agents supports an overall protective effect of anti-TNF therapies on lifetime risk of diabetes as well as insulin sensitivity and obesity.[74]

A recent large proof of concept trial of anti-inflammatory therapy in patients after myocardial infarction (A Randomized, Double-blind, Placebo-controlled, Event-driven Trial of Quarterly Subcutaneous Canakinumab in the Prevention of Recurrent Cardiovascular Events Among Stable Post-Myocardial Infarction Patients With Elevated hsCRP [CANTOS]; canakinumab targeting IL-1β) showed a clear reduction in the rate of cardiovascular events, albeit with an associated increase in the rate of severe infections.[78] These results were particularly evident in high-risk patients, although effects on metabolic profile remain unclear.[78] However, evidence that IL-1β targeting may have significant metabolic benefits has been well established, as evidenced by improved profile insulin sensitivity in response to IL1-β blockade.[79] The potential beneficial effects of anti-inflammatory and immune-modulating agents in T2D and its complications may relate to direct vasoprotective effects. These studies have led to the rapid development of the concept of immunometabolism, clearly linking metabolic changes in the tissues to the regulation of inflammation as well as metabolic status of immune cells to their activation.[28,56] The latter can be characterized by a switch between oxidative phosphorylation and anaerobic glycolysis, which is observed in macrophages and T cells.[30,59] This also emphasizes the importance of the interplay between vascular oxidative stress and the development of inflammation in adipose tissue and the vasculature.

Anti-inflammatory properties of antidiabetic therapies. Classic approaches improving metabolic health, such as weight reduction and the use of metformin, statin drugs, pioglitazone, and insulin have been shown to have anti-inflammatory effects. Metformin reduces C-reactive protein levels by 13%. More recently, a novel anti-inflammatory mechanism of metformin affecting M1/M2 polarization of macrophages has been shown to reduce obesity-associated low-grade inflammation, possibly because of adenosine monophosphate-activated protein kinase (AMPK) activation. These effects were modulated by AMPK and the AMPK analogue 5-aminoimidazole-4-carboxamide ribonucleotide, effects that appear stronger than those of metformin.[80] Recent studies have shown that salicylates have anti-inflammatory effects that involve inhibition of NF-κB and that they also prevent diabetes and improve insulin resistance in experimental models and humans.[81,82] Drugs such as glicazide and troglitazone, as well as N-acetylcysteine, decrease inflammatory markers in patients with diabetic nephropathy and diabetic retinopathy.[83]

Epigenetics is another mechanism that may influence inflammation and immunometabolism in diabetes.[59] Histone deacetylase (HDAC) inhibitors cause NF-κB inhibition through acetylation of the p65 subunit. Givinostat (formerly ITF2357), an orally active HDAC inhibitor, has been shown to prevent the development of diabetes.[84,85] Similarly, activation of sirtuin1, which is involved in inflammation, metabolism, and aging, has been shown to have anti-inflammatory properties in diabetes.[86]

MiRNAs, Diabetes, and Vascular Complications

miRNAs are a group of noncoding RNAs that are multifunctional. They fine tune gene expression and have been implicated in various pathologic processes, including T2D and the development of diabetic vascular complications. A number of pancreatic B-cell—specific miRNAs have been identified, including miR-375, miR-124a, miR-96, miR-7a, miR7a2, miR-30d, miR-9, miR-200, miR-184, and let-7.[87] These play a role in pancreatic function, insulin secretion, and glucose tolerance. Differential miRNA signatures have been identified among prediabetic individuals, patients with diabetes, and patients with diabetes and vascular complications, suggesting that miRNAs may be novel biomarkers. Diabetic cardiovascular complications are associated with increased levels of miR-223, miR-320, miR-501, miR504, and miR1 and decreased levels of miR-16, miR-133, miR-492, and miR-373.[9] Whether these changes in miRNA are simply biomarkers of disease or whether they are directly involved in the vasculopathy of diabetes remains unclear.

Treatment of diabetes mellitus and its cardiovascular complications

Once T2D has been diagnosed, the aim of achieving glucose control is principally to avoid microvascular complications. There are some benefits with respect to macrovascular complications, but this is dependent on the profile of individual drug classes and even appears to be different for agents within the same class.[88] The role of BP lowering to improve prognosis in T2D has been established since the **UK P**rospective **D**iabetes **S**tudy (UKPDS) in 1998.[89,90] However, more recently, more widespread use of glucose-lowering agents that reduce (rather than increase) weight, lower BP, and have beneficial "off-target" effects (as demonstrated in recent large cardiovascular outcome trials) facilitates cardiovascular risk factor control and is playing a role in improving the cardiovascular prognosis of T2D.[91,92]

Achieving glucose control in T2D begins with weight management. Particularly in the first 8 years after diagnosis, normal glucose tolerance can be restored if radical weight reduction can be achieved, most effectively using a very low

calorie liquid replacement diet.[93] In obese patients, this can also occur after successful bariatric surgery, particularly the Roux-en-Y procedure.[94] The mechanism may involve reduction in ectopic fat, and consequent relief from its proinflammatory effects, in and around the pancreatic islets of Langerhans.[95]

All current glucose-lowering guidelines suggest the early addition of metformin as first-line therapy. Unlike the sulphonylureas, which augment insulin secretion, metformin lowers blood glucose levels principally by decreasing hepatic glucose production and promoting weight reduction (with little effect on BP). Among the many proposed mechanisms of action of metformin is activation of AMPK: This is now thought to be a secondary effect of inhibition of the mitochondrial respiratory chain.[96] Such effects of metformin may act directly (ie, independent of blood glucose lowering) on other tissues, including vascular endothelial cells. Metformin treatment is associated with improvements in endothelial biomarkers and reduction in plasma high-sensitivity C-reactive protein levels.[97,98] It was associated with cardiovascular benefit in the landmark UKPDS.[99]

Other second-line agents used in glucose lowering include pioglitazone, a thiazolidinedione that directly promotes the differentiation of adipocytes within subcutaneous adipose depots (by activation of peroxisome proliferator-activated receptor-γ), thus promoting storage of non-esterified fatty acids (NEFAs).[100] Pioglitazone reverses many of the metabolic features associated with insulin resistance without much effect on BP. Anti-inflammatory effects have been demonstrated in human adipose tissue biopsy samples and also in some animal models.[101] There was great hope in the 1990s that agents from this class would have major benefits for the cardiovascular system, a hypothesis that was to some extent supported by the results of the **Pro**spective Pioglit**a**zone **C**linical Trial in Macro**v**ascular **E**vents (PROACTIVE) cardiovascular outcome trial, although beneficial effects were offset by weight gain and fluid retention.[102]

More recently introduced classes of glucose-lowering agents have heralded an exciting era in T2D pharmacotherapy because they are associated with weight reduction, BP reduction, and, importantly, reduced rates of major adverse events in long-term cardiovascular outcome trials.[91,92,103]

Glucagon-like peptide-1 agonists are injectable agents that augment glucose-dependent insulin secretion (the "incretin" effect), delay gastric emptying (enhancing satiety), and have central effects on hypothalamic nuclei to reduce appetite.[104] Systolic BP is lowered beyond the effect that would be expected purely from weight loss, and there is an improvement in pulse-wave velocity, reflecting a reduction in arterial stiffness. However, the time course of cardiovascular event reduction in the **L**iraglutide **E**ffect and **A**ction in **D**iabetes: **E**valuation of Cardiovascular Outcome **R**esults (LEADER) trial suggests a primary antiatherosclerotic rather than hemodynamic effect.[91] Indeed, liraglutide has been shown to have anti-inflammatory actions on the cardiovascular system in a number of preclinical and clinical studies.[103,105]

SGLT2 inhibitors promote lowering of the threshold for urinary glucose excretion: an additional glucose equivalent to 300 kcal per day is therefore cleared by the kidneys, promoting weight loss and a catabolic state with increased circulating ketone bodies and NEFAs.[106] There are associated reductions in BP and plasma volume, which together may have been responsible for the early reduction in cardiovascular event rates seen with empagliflozin in Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial.[91] A shift in fuel substrate metabolism from glucose to NEFAs and ketones, including by the myocardium, is 1 of the mechanisms by which SGLT2 inhibitors may provide cardiovascular protection,[107] but studies in apoE knockout mice and Zucker diabetic fatty rats suggest that anti-inflammatory effects may also play a role.[108]

Diabetes, vasoprotection, and potential new therapies

Data from landmark clinical trials in T2D including UKPDS, ADVANCE, and **A**ction to **C**ontrol **C**ardi**o**vascular **R**isk in **D**iabetes (ACCORD) demonstrate that treating comorbidities including hypertension and hypercholesterolemia is a more effective strategy for reducing cardiovascular complications than targeting blood glucose levels with conventional agents.[109] Antihypertensive drugs such as angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, mineralocorticoid-receptor blockers, and calcium-channel blockers may have direct vasoprotective effects, and their use may contribute, at least in part, to reduced vascular complications in patients with diabetes and concomitant hypertension.[110] Tight control of BP has been shown to reduce cardiovascular risk in T2D: most recent US and Canadian guidelines recommend a target of $< 130/80$ mm Hg.[111,112] Statin drugs and clopidrogel are also vasoprotective and may have extra benefit in patients with diabetes. Some of the beneficial effects of these drugs have been attributed to their antioxidant and anti-inflammatory properties.

New therapeutic approaches targeting oxidative stress, inflammation, and fibrosis are currently being developed to treat diabetes-associated cardiovascular complications.[113] In particular, drugs that increase Nrf-2 activity, such as bardoxolone methyl, and strategies to inhibit the pyrin domain containing 3 (NLRP3) inflammasome, may have therapeutic potential. A novel bardoxolone methyl derivative, dh404, has been shown to attenuate endothelial dysfunction, reduce Nox1 expression, decrease oxidative stress, and inhibit inflammation in diabetic mice, suggesting that upregulation of Nrf2 may have therapeutic potential to limit diabetes-associated vascular damage.[114] Another example includes inhibition of dipeptidyl peptidase-4 by linagliptin, which reduces obesity-related insulin resistance and inflammation by regulating M1/M2 macrophage status.[115] Other therapies on the horizon for the treatment of cardiovascular complications of diabetes include pentoxifylline (methylxanthine derivative and nonspecific phosphodiesterase inhibitor with anti-inflammatory and antifibrotic effects), ruboxistaurin (selective protein kinase C-β inhibitor), pirfenidone (TGF-β inhibitor), bindarit (MCP-1/CCL2 inhibitor), sulodexide (an oral formulation composed of 2 glycosaminoglycans), AKB-9778 (Tie2 activator), baricitinib (JAK/STAT inhibitor), and Nox inhibitors.[116] The clinical benefit of these compounds awaits further confirmation, and novel nanotherapeutic approaches are being developed to target inflammation.[117]

Conclusions

Diabetes is associated with an increased risk of CVD, which is exaggerated with coexistent hypertension. Many of the underlying molecular mechanisms, including oxidative stress, inflammation, and fibrosis causing microvascular and macrovascular complications of diabetes, also cause vascular remodelling and dysfunction in hypertension. Controlling comorbidities, especially hypertension, and targeting strategies to promote vascular health, may be especially important in reducing the microvascular and macrovascular complications of diabetes.

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Disclosures

The authors have no conflicts of interest to disclose.

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Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials

M R Law, N J Wald, J K Morris, R E Jordan

Abstract

Objective To determine the average reduction in blood pressure, prevalence of adverse effects, and reduction in risk of stroke and ischaemic heart disease events produced by the five main categories of blood pressure lowering drugs according to dose, singly and in combination.

Design Meta-analysis of 354 randomised double blind placebo controlled trials of thiazides, β blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, and calcium channel blockers in fixed dose.

Subjects 40 000 treated patients and 16 000 patients given placebo.

Main outcome measures Placebo adjusted reductions in systolic and diastolic blood pressure and prevalence of adverse effects, according to dose expressed as a multiple of the standard (recommended) doses of the drugs.

Results All five categories of drug produced similar reductions in blood pressure. The average reduction was 9.1 mm Hg systolic and 5.5 mm Hg diastolic at standard dose and 7.1 mm Hg systolic and 4.4 mm Hg diastolic (20% lower) at half standard dose. The drugs reduced blood pressure from all pretreatment levels, more so from higher levels; for a 10 mm Hg higher blood pressure the reduction was 1.0 mm Hg systolic and 1.1 mm Hg diastolic greater. The blood pressure lowering effects of different categories of drugs were additive. Symptoms attributable to thiazides, β blockers, and calcium channel blockers were strongly dose related; symptoms caused by ACE inhibitors (mainly cough) were not dose related. Angiotensin II receptor antagonists caused no excess of symptoms. The prevalence of symptoms with two drugs in combination was less than additive. Adverse metabolic effects (such as changes in cholesterol or potassium) were negligible at half standard dose.

Conclusions Combination low dose drug treatment increases efficacy and reduces adverse effects. From the average blood pressure in people who have strokes (150/90 mm Hg) three drugs at half standard dose are estimated to lower blood pressure by 20 mm Hg systolic and 11 mm Hg diastolic and thereby reduce the risk of stroke by 63% and ischaemic heart disease events by 46% at age 60-69.

Introduction

Lowering systolic blood pressure by 10 mm Hg or diastolic blood pressure by 5 mm Hg reduces the risk of stroke by about 35% and that of ischaemic heart disease (IHD) events by about 25% at age 65.[1–3] This applies across all levels of blood pressure in Western populations, not only in "hypertension."[1–7] Blood pressure lowering drugs should be more widely used,[6 7] but which drugs are most appropriate, whether combinations of drugs should be used routinely, and whether lower doses than those currently used are preferable is not known. Large trials and systematic reviews have not examined the effects of variation in dose or of combination treatment.[8–10] We report a systematic review of randomised placebo controlled trials of the five main categories of blood pressure lowering drugs to answer these questions.

Methods

We sought randomised placebo controlled trials that recorded the change in blood pressure in relation to a specified fixed dose of any thiazide, β blocker, angiotensin converting enzyme (ACE) inhibitor, angiotensin II receptor antagonist, or calcium channel blocker. We searched the Medline, Cochrane Collaboration, and Web of Science databases. Details of the search procedure are on www.smd.qmul.ac.uk/wolfson/bpchol. We used the same set of 354 trials identified and reported in our *Health Technology Assessment* monograph on the quantification of standard dose blood pressure treatment.[7] In this paper we examine the effect of dose and combination treatment on efficacy and adverse effects. With the exceptions below we included all double blind trials, irrespective of the age or diseases of the participants. Most participants had high blood pressure (typically 90-110 mm Hg diastolic), but trials of people with non-vascular conditions (such as thiazides for renal stones) provided evidence of efficacy at lower blood pressures.

We excluded trials with no placebo group, under two weeks' duration, titrating dose so that different patients received different doses, treating some control patients, testing drugs only in combination with other drugs, with non-randomised order of treatment and placebo periods in crossover trials, with most participants black (because of their different responses to some blood pressure lowering drugs[11]), or recruiting

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References to studies included and a table appear on bmj.com

patients with heart failure, acute myocardial infarction, or other cardiovascular disorders. We included 354 trials.[w1-w343]

We defined the efficacy of a drug as the reduction in systolic and diastolic blood pressure for a specified dose, expressed as the change in the treated group minus that in the placebo group (in crossover trials end treatment minus end placebo blood pressure). We categorised reductions in blood pressure as "peak" (2-6 hours after the last dose) or "trough" (22-26 hours; we did not include trough data from trials of drugs taken more than once daily[7]). Blood pressure was recorded sitting or supine.

In combining trial data we specified equivalent daily doses of different drugs as the "usual maintenance dose" in reference pharmacopoeias.[12–14] We call this the standard dose. Where a range was given we took the lower dose as the standard dose.

We analysed the data by using Stata software. Parallel group trials and crossover trials yielded similar results, so we combined them. We fitted random effects regression models (separately for systolic and diastolic blood pressure) relating change in blood pressure in each treatment arm (treated minus placebo), weighted by the inverse of its variance, to category of drug, dose (expressed as a proportion of the standard dose), usual pretreatment blood pressure (estimated as that in the placebo group at the end of the trial to avoid regression to the mean), whether blood pressure measurements were peak or trough, and average age. We estimated the variance of the change in blood pressure, if not directly reported, from the standard error of blood pressure before and after the intervention as described previously.[15] Data to calculate the variance were unavailable in 45 trials; we estimated it, given the number of participants, from the average in all parallel group and crossover trials reporting variance.

The fit of the model was better with the dose expressed on a logarithmic (proportional) scale rather than on a linear scale, meaning that a halving of a dose was taken as equivalent to a doubling. We used straight lines (a quadratic fit was no better), so if fall in blood pressure was a at standard dose and $a+b$ at twice standard dose, it would be $a-b$ at half standard dose. We thereby obtained placebo adjusted estimates of the blood pressure lowering effect of each category of drug according to dose. We compared these by using the indirect method.[16]

We estimated adverse effects attributable to the drugs as the difference in prevalence between treated and placebo groups in respect of the numbers of participants reporting one or more symptoms in trials recording all symptoms that might be drug related (313 of the 354 trials, 88% of all participants in the 354 trials) and the numbers of participants who stopped taking the tablets because of symptoms (305 trials, 84% of all participants). We excluded headache because published evidence, and our own analysis, showed that fewer treated patients than placebo patients reported it.[17] Adverse metabolic effects recorded were changes in serum cholesterol and its subfractions, potassium, glucose, and uric acid. The fit of the data to the model was again better with dose expressed on a logarithmic scale than a linear scale. We weighted the differences between treated and placebo groups in biochemical changes by the inverse of the variance and the differences in the proportions developing symptoms by the numbers of participants in the treated (n_1) and placebo (n_2) groups, as the inverse of $\sqrt{(1/n_1^2 + 1/n_2^2)}$.

We analysed data on whether the combined effect of two drugs of different categories was additive with respect to blood pressure reduction and adverse effects. Within the 354 trials 50 trials (119 comparisons) tested the effect of drugs of two different categories separately and in combination. Of 238 treatment groups 84 tested thiazides, 26 β blockers, 71 ACE inhibitors, 3 angiotensin II receptor antagonists, 44 calcium channel blockers, and 10 other drugs. We combined the 119 comparisons, weighting each by the inverse of its variance.

Table 1 Details of the 354 trials of blood pressure lowering drugs (adapted from Law et al[7])

	Treatment	Placebo
No of participants (No of different drugs) in trials of:		
Thiazides (7)	4 502	2 636
β blockers (15)	5 189	2 701
ACE inhibitors (12)	9 350	4 712
Angiotensin II receptor antagonists (8)	12 840	5 100
Calcium channel blockers (11)	7 998	3 976
All trials	39 879	15 817*
No of treatment groups within trials of:		
Thiazides	104	64
β blockers	136	76
ACE inhibitors	217	114
Angiotensin II receptor antagonists	125	54
Calcium channel blockers	209	122
All trials	791	354*
Trial design:		
Crossover	219	125
Parallel group	572	229
Mean (90% range) pretreatment blood pressure (mm Hg):		
Systolic	154 (139-170)	154 (139-170)
Diastolic	97 (87-106)	97 (87-106)
Median (90% range) duration (weeks)	4 (2-12)	4 (2-12)
Mean (90% range) age (years)	53 (43-68)	53 (43-68)

ACE=angiotensin converting enzyme.
*Less than total of five categories because some trials compared drugs from two or more categories with the same placebo group.

Results

Table 1 shows details of the 354 randomised trials identified.[w1-w343] The trials included 791 treatment groups, testing different drugs or different doses of the same drug, with about 40 000 participants receiving treatment and 16 000 receiving placebo. Tables giving further information on the 354 individual trials and the standard doses and costs of the drugs are on www.smd.qmul.ac.uk/wolfson/bpchol

Efficacy

Single drugs

Figure 1 shows the dose-response relations for the five categories of blood pressure lowering drug for systolic pressure (the plots for diastolic pressure were similar). The blood pressure reductions are the average of the peak and trough estimates and are placebo adjusted. The straight lines fit the data well.

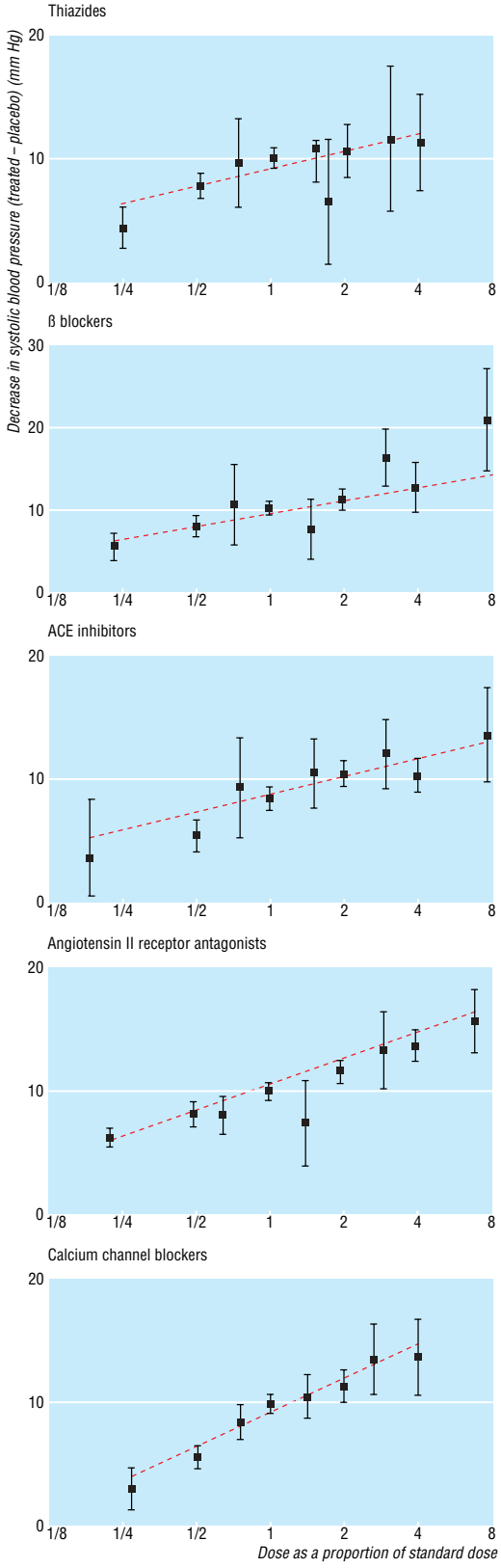

Fig 1 Average reductions in systolic blood pressure (adjusted for the change in the placebo group; with 95% confidence intervals) according to category of drug and dose as a proportion of standard (designated 1), from the results of 354 randomised trials, with the best fitting line. ACE=angiotensin converting enzyme

Table 2 shows the average reductions in blood pressure over 24 hours produced by half standard, standard, and twice standard doses of the five categories of drug. Within each dose category the reductions were remarkably similar for different categories of drugs; few statistically significant differences existed, and no category of drug was materially more effective than another. Reductions with half standard dose were about 20% less than those with standard dose.

The individual drugs within each of the five categories produced similar reductions in blood pressure. No more "statistically significant" differences occurred than would be expected with so many comparisons. Some drugs may be more effective than others, but any differences are small, and in the absence of any prior hypothesis we could not identify them. The cheaper drugs within each category were as effective as the more expensive ones.

Within each of the five categories the average reductions in systolic and diastolic blood pressure recorded showed statistically significant heterogeneity across trials (greater variation than expected through chance). On average, 78% of the variance between trials in the reduction in systolic blood pressure and 69% of that in diastolic pressure were explained by the combined effects of differences in dose (as a proportion of standard), pretreatment blood pressure (see below), whether blood pressure was peak or trough, and differences between individual drugs (standard doses of different drugs within a category will not correspond exactly to equivalent pharmacological effects, and some drugs within a category may genuinely be better than others). We could not quantify differences between trials in proportions of participants who adhered to the protocol and in the extent to which non-adherent patients were included in the results or the effect of age.

Figure 2 shows that the drugs significantly lowered blood pressure from all pretreatment levels, although the reduction was greater (in absolute and proportional terms) from a higher level. The relation was well fitted by a straight line. If the pretreatment blood pressure was 10 mm Hg higher, the reduction in blood pressure with one drug at standard dose increased on average by 1.0 (95% confidence interval 0.7 to 1.2) mm Hg systolic and 1.1 (0.8 to 1.4) mm Hg diastolic. The blood pressure reductions shown in table 2 apply to the average pretreatment blood pressure in all the trials of 154 mm Hg systolic and 97 mm Hg diastolic. No effect of age was evident, but age varied little across trials.

Combinations of drugs

Fifty trials (including 119 placebo controlled comparisons) compared drugs from two categories, separately and together. Figure 3 shows the observed placebo adjusted reductions in blood pressure with two drugs taken together plotted against the expected reductions from adding the reductions produced by each drug alone. Overall the points lie close to the 45° line of identity between observed and expected across a wide range of blood pressure reductions. Table 3 shows that the sum of the average reductions in blood pressure with each drug used alone is close to the observed effect of the two drugs used in combination, indicating

Table 2 Efficacy: average reductions* in blood pressure over 24 hours (treated minus placebo) according to category of drug and dose

Category of drug†	Fall in blood pressure (mm Hg) (95% CI)			Half standard *v* standard: proportional difference (%)
	Half standard dose	Standard dose	Twice standard dose	
Systolic blood pressure				
Category:				
Thiazides	7.4 (6.6 to 8.2)	8.8 (8.3 to 9.4)	10.3 (9.4 to 11.2)	16
β blockers	7.4 (6.6 to 8.3)	9.2 (8.6 to 9.9)	11.1 (10.2 to 12.0)	20
ACE inhibitors	6.9 (6.1 to 7.8)	8.5 (7.9 to 9.0)	10.0 (9.5 to 10.4)	19
Angiotensin II receptor antagonists	7.8 (7.1 to 8.6)	10.3 (9.9 to 10.8)	12.3 (11.7 to 12.8)	24
Calcium channel blockers	5.9 (5.2 to 6.6)	8.8 (8.3 to 9.2)	11.7 (11.0 to 12.3)	33
All categories: average	7.1 (6.8 to 7.5)	9.1 (8.8 to 9.3)	10.9 (10.7 to 11.2)	22
Diastolic blood pressure				
Category:				
Thiazides	3.7 (3.2 to 4.2)	4.4 (4.0 to 4.8)	5.0 (4.4 to 5.7)	16
β blockers	5.6 (5.0 to 6.2)	6.7 (6.2 to 7.1)	7.8 (7.1 to 8.4)	16
ACE inhibitors	3.7 (3.2 to 4.2)	4.7 (4.4 to 5.0)	5.7 (5.4 to 6.0)	21
Angiotensin II receptor antagonists	4.5 (4.2 to 4.8)	5.7 (5.4 to 6.0)	6.5 (6.2 to 6.8)	21
Calcium channel blockers	3.9 (3.5 to 4.4)	5.9 (5.6 to 6.2)	7.9 (7.5 to 8.3)	34
All categories: average	4.4 (4.2 to 4.6)	5.5 (5.4 to 5.7)	6.5 (6.3 to 6.7)	20

ACE=angiotensin converting enzyme.
*Estimates are average over 24 hours from combining separate peak and trough estimates.
†Examples of standard daily dose of one drug in each category: bendroflumethazide 2.5 mg, atenolol 50 mg, lisinopril 10 mg, valsartan 80 mg, amlodipine 5 mg. See www.smd.qmul.ac.uk/wolfson/bpchol for standard doses of all drugs.

an additive effect. The 119 comparisons showed an additive effect for six of the 10 possible combinations. Only one trial (which was inconclusive) studied β blockers with ACE inhibitors,[w76] and no trial used angiotensin II receptor antagonists with drugs other than thiazides. The independent effects on blood pressure are not surprising as the different categories of drugs have different modes of action, apart from ACE inhibitors and angiotensin II receptor antagonists (and even these may have additive effects[18]). Although no trial has studied the effect of three drugs in combination, the additive effect of many combinations of two drugs suggests that the effect of three drugs in combination would also be additive.

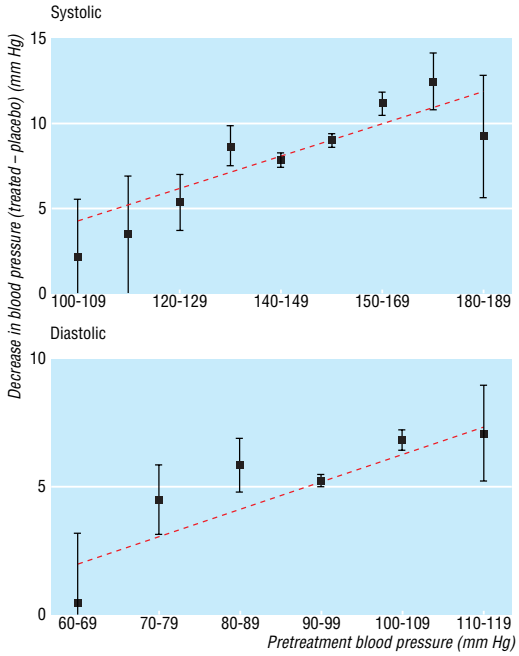

Fig 2 Average reduction in blood pressure (adjusted for the change in the placebo group; with 95% confidence intervals) according to the usual pretreatment blood pressure, from the results of 354 randomised trials, with the best fitting line

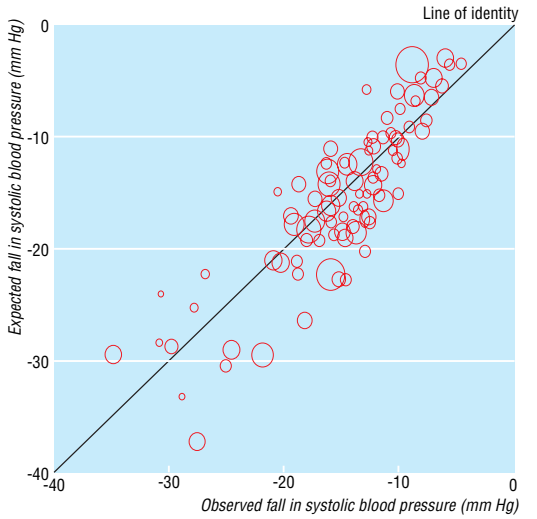

Fig 3 Trials testing two blood pressure lowering drugs separately and in combination: observed placebo adjusted reduction in systolic blood pressure (treated minus placebo) with two drugs used in combination plotted against the expected reduction in blood pressure from adding the reductions produced by each drug alone. The area of each symbol is inversely proportional to the variance in the trial it represents. Adapted from Law et al[7]

Table 4 shows the expected reduction in blood pressure with one, two, and three blood pressure lowering drugs used at half standard dose. The reductions are adjusted from those in table 2 to a usual pretreatment blood pressure of 150/90 mm Hg, which cohort studies show is about average in people who have a stroke or IHD event.[7] The reductions with two and three drugs are based on the additive effect (table 3) but adjusted for the lower pretreatment blood pressure for each successive drug (fig 2). Three drugs together would be expected to lower blood pressure by about 20 mm Hg systolic and 11 mm Hg diastolic.

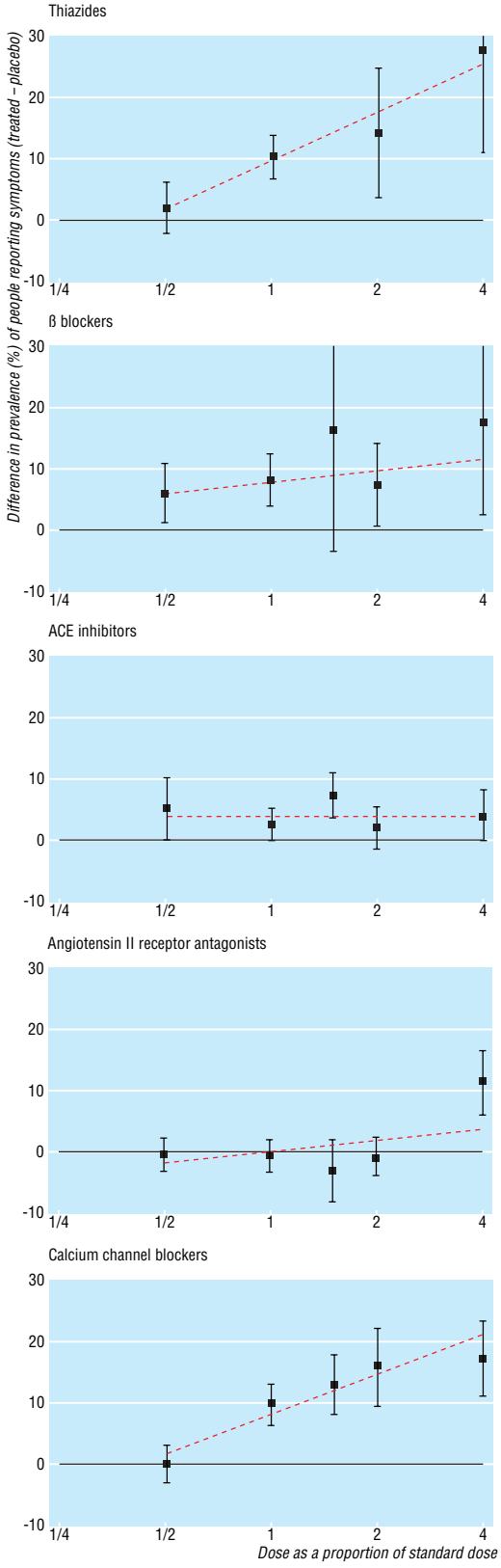

Fig 4 —Proportions of people reporting one or more symptoms attributable to treatment (treated minus placebo; with 95% confidence interval) according to category of drug and dose as a proportion of standard (designated 1). ACE=angiotensin converting enzyme

Table 3 Efficacy: effects of two different drugs on blood pressure separately and in combination (summary results from 119 randomised placebo controlled comparisons; adapted from Law et al[7])

	Average (SE) fall in blood pressure (mm Hg) (treated minus placebo)	
Treatment	**Systolic**	**Diastolic**
Observed		
"First" drug alone	7.0 (0.4)	4.1 (0.3)
"Second "drug alone	8.1 (0.3)	4.6 (0.3)
Both drugs together	14.6 (0.5)	8.6 (0.4)
Expected		
Sum of first and second drugs alone	15.1	8.7
Difference between observed and expected (95% CI)	–0.5 (–1.4 to 0.4)	–0.1 (–1.0 to 0.8)

Table 4 Efficacy: blood pressure lowering effects of drugs when used at half standard dose separately and in combination

	Blood pressure reduction* (95% CI)		
	One drug	**Two drugs**	**Three drugs**
Systolic blood pressure (mm Hg)	6.7 (6.1 to 7.2)	13.3 (12.4 to 14.1)	19.9 (18.5 to 21.3)
Diastolic blood pressure (mm Hg)	3.7 (3.1 to 4.3)	7.3 (6.2 to 8.3)	10.7 (9.1 to 12.4)

*Reductions in blood pressure adjusted to a usual pretreatment blood pressure of 150/90 mm Hg, the average blood pressure in people aged 50-69 years who have a stroke or ischaemic heart disease event.[7]

Adverse effects

Single drugs

Figure 4 shows the difference in the proportions of participants who experienced one or more symptoms between treated and placebo groups according to dose. The straight lines generally fit the data well, and a clear dose-response relation can be seen for three categories of drugs. Table 5, based on the straight lines in figure 4, shows that thiazides and calcium channel blockers caused symptoms infrequently (2.0% and 1.6%) at half standard dose but commonly (9.9% and 8.3%) at standard dose (P (for trend) <0.001). β blockers caused symptoms in 5.5% of patients at half standard dose and in 7.5% at standard dose (P=0.04). Cough (3.9%) was virtually the only symptom with ACE inhibitors and did not vary with dose, a finding consistent with earlier studies.[19,20] No excess of symptoms occurred at standard dose or half standard dose of angiotensin II receptor antagonists; in particular, no excess of cough occurred.[7]

Trials of crossover design showed that symptoms are reversible on stopping the drugs. The trials in this analysis were short (a few weeks), but one trial showed that the prevalence of symptoms caused by a thiazide or a β blocker (treated minus placebo) was in general no greater after two years than after 12 weeks.[21] Thiazides were the only drugs to affect sexual function, a finding confirmed in a large long term trial.[22]

The prevalence of symptoms sufficiently severe to stop treatment (treated minus placebo) was 0.8% (0.3% to 1.4%) for β blockers, 0.1% for thiazides and ACE inhibitors, and zero for angiotensin II receptor antagonists (table 6). Sufficient trial data were available for calcium channel blockers to allow examination of a dose effect: no excess risk occurred at half standard dose (table 6), but the risk was 1.4% (0.4% to 2.4%) at standard dose and 4.5% (2.4 to 6.6%) at twice standard dose.

The metabolic effects of thiazides were dose dependent (table A on bmj.com). The increase in serum cholesterol was 1% at half standard dose, 3% at

Table 5 Adverse effects of drugs: percentage of people with one or more symptoms attributable to treatment*, according to category of drug and dose, in randomised trials

Category of drug	No of trials	Percentage (95% CI) with symptoms (treated minus placebo)†		
		Half standard dose	Standard dose	Twice standard dose
Thiazides	59	2.0 (–2.2 to 6.3)	9.9 (6.6 to 13.2)	17.8 (11.5 to 24.2)
β blockers	62	5.5 (0.3 to 10.7)	7.5 (4.0 to 10.9)	9.4 (3.6 to 15.2)
ACE inhibitors	96	3.9 (–3.7 to 11.6)	3.9 (–0.5 to 8.3)	3.9 (–0.2 to 8.0)
Angiotensin II receptor antagonists	44	–1.8 (–10.2 to 6.5)	0 (–5.4 to 5.4)	1.9 (–5.6 to 9.3)
Calcium channel blockers	96	1.6 (–3.5 to 6.7)	8.3 (4.8 to 11.8)	14.9 (9.8 to 20.1)

ACE=angiotensin converting enzyme.
*Calculated as difference between treated and placebo groups in proportion of participants who developed one or more symptoms, excluding headaches, which were significantly less common in people receiving treatment.
†Commonest symptoms: thiazides—dizziness, impotence, nausea, muscle cramp; β blockers—cold extremities, fatigue, nausea; ACE inhibitors—cough; calcium channel blockers—flushing, ankle oedema, dizziness.[7]

standard dose, and 5% at twice standard dose. Thiazides did not materially affect low density lipoprotein cholesterol or high density lipoprotein cholesterol; the increase was in the very low density lipoprotein subfraction, which is associated only weakly with atherogenesis.

Thiazides at half standard dose also had a small effect in decreasing serum potassium (−6%), increasing blood glucose (1%), and increasing serum uric acid (9%) (table A on bmj.com). Even at standard doses the loss of total body potassium is small (about 200 mmol/l) and does not increase the risk of cardiac arrhythmia.[7 23–27] The increase in blood glucose is reversible, with no excess risk of overt diabetes.[28 29] From the association between serum uric acid and gout reported in a cohort study of men (adjusted for age and other confounding factors), the 9% average increase in uric acid at half standard dose would be expected to increase the incidence of gout by 58% (45% to 71%), from a background incidence of about 1.5 per 1000 per year to 2.4 per 1000 per year (an absolute increase of under 1 per 1000 per year).[30 31] Gout is less common in women,[31] and the absolute increase would be about 1 per 10 000 per year.

Insufficient data were available to examine the effect by dose for the other four drug categories.[7] In six trials of β blockers (average dose was 1.4 × standard) total serum cholesterol decreased by 3%, comprising separate small decreases in low density and high density lipoprotein cholesterol (similar to a previous finding[32]). β blockers produced a 2% (1% to 4%) increase in serum potassium on average (10 trials) and no significant change in blood glucose or uric acid.[7] ACE inhibitors and angiotensin II receptor antagonists increase serum potassium because of their effect on aldosterone: in 18 trials of either the average increase was 3% (2% to 5%). Calcium channel blockers did not increase blood glucose (95% confidence interval 2% lower to 5% higher; 10 trials), and no increase in diabetes occurred in a six year study.[28]

Combinations of drugs

Of the 50 placebo controlled trials testing drugs of two different categories separately and in combination, 33 reported adverse effects. In 66 trial arms single drugs caused symptoms in 5.2% (3.6% to 6.6%) of participants on average (prevalence in treated group minus placebo). In 33 trial arms two drugs together caused symptoms in 7.5% (5.8% to 9.3%), which is significantly lower than the value of 10.4% (twice 5.2%) expected with an additive effect (P=0.03). One drug does not therefore potentiate the adverse effects of another. The lower than expected prevalence with two drugs may suggest that some people are more likely than others to either experience or report symptoms.

In trials testing different drugs separately and together the serum potassium lowering effect of thiazides was offset by β blockers,[w29,w36,w39,w51] ACE inhibitors,[w4,w26,w34] and angiotensin II receptor antagonists.[w30]

Table 6 Adverse effects of drugs: percentage of people with symptoms attributable to treatment sufficient to stop taking the tablets, according to category of drug in randomised trials (adapted from Law et al[7])

Category of drug	No of trials	Average dose as multiple of standard	Percentage (95% CI) who stopped taking tablets because of symptoms (treated minus placebo)
Thiazides	57	1.0	0.1 (–0.7 to 0.9)*
β blockers	62	1.3	0.8 (0.3 to 1.4)
ACE inhibitors	92	1.9	0.1 (–0.3 to 0.6)*
Angiotensin II receptor antagonists	44	1.3	–0.2 (–0.5 to 0.2)*
Calcium channel blockers	92	0.5	–1.3 (–2.6 to 0.0)*

ACE=angiotensin converting enzyme.
*Not statistically significant; however, upper confidence interval is informative.

Discussion

The five categories of drugs produced similar reductions in blood pressure and were effective from all pretreatment levels (fig 2), reinforcing the view that use of blood pressure lowering drugs should be determined by a person's overall level of risk rather than the blood pressure alone.[6] Reduction in blood pressure was only about 20% less at half standard dose than at standard dose, but adverse effects were much less common. Efficacy of drugs in combination was additive, but prevalence of adverse effects was less than additive. Combinations of two or three drugs at low dose are therefore preferable to one or two drugs at standard dose. Within each category no one drug was better than another; choice of drug should be based on low cost and once daily administration. Everyone at increased risk would benefit from using three drugs, apart from those with contraindications to a particular drug.

Table 7 shows the expected reductions in the incidence of stroke and IHD events from using blood pressure lowering drugs at half standard dose separately and in combination. The calculations used the blood pressure reductions from table 4 and the estimates of the association between blood pressure and disease events at age 60-69 from the Prospective Studies Collaboration (these are similar to those from

Table 7 Effects of blood pressure lowering drugs on reducing the incidence of stroke and ischaemic heart disease events when used separately and in combination at half standard dose*

Disease	Percentage (95% CI) reduction in incidence		
	One drug	Two drugs	Three drugs
Stroke	29 (26 to 31)	49 (42 to 55)	63 (55 to 70)
Ischaemic heart disease events	19 (17 to 21)	34 (29 to 40)	46 (39 to 53)

*Calculated from reductions in blood pressure in table 4 and estimates of association between blood pressure and disease events at age 60-69 years from the Prospective Studies Collaboration.[1]

What is already known on this topic

Blood pressure lowering drugs prevent stroke and heart disease, but whether they are best used in combination, and if so at what dose, is not known

What this study adds

The efficacies of five categories of drug are similar at standard doses and only 20% lower at half standard doses; adverse effects are much less common at half standard dose than at standard dose

The drugs are effective from all pretreatment levels of blood pressure

Reductions in blood pressure with drugs in combination are additive; adverse effects are less than additive

Using three blood pressure lowering drugs in low dose combination would reduce stroke by two thirds and heart disease by half

other pooled cohort study data and meta-analyses of randomised trials).[1–4 7] The estimates are based on diastolic pressure, but those based on the average of systolic and diastolic pressures (probably the best measure to use[1]) are similar. Three drugs in combination at half standard dose reduce the risk of stroke by 63% and IHD events by 46%. Use of one of the three drugs at standard dose (an ACE inhibitor or angiotensin II receptor antagonist because adverse effects were no higher at standard than half standard dose) reduces blood pressure by a further 2.3 mm Hg systolic and 1.0 mm Hg diastolic and reduces the risk of stroke by 66% and IHD events by 49%.

All but two of our conclusions are based on direct evidence. No trial directly studied the combined effect of three drugs on blood pressure, but an additive effect follows because an additive effect has been shown for many combinations of two drugs. Randomised trials have not tested the combined effect of two or three drugs on the incidence of stroke and IHD events, but the cohort studies show a continuous relation between blood pressure and the risk of these diseases,[1–3] confirmed by randomised trials of single drug treatment from a wide range of pretreatment levels.[4–7]

Three drugs in low dose combination have a large preventive effect, reducing the risk of stroke by two thirds and IHD events by half, with a low prevalence of adverse effects. Low dose combination treatment should be used as a first option in lowering blood pressure, and the indications for using blood pressure lowering drugs should be broadened.

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Latin American Consensus on the management of hypertension in the patient with diabetes and the metabolic syndrome

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The prevalence of hypertension, type 2 diabetes mellitus (DM2) and the metabolic syndrome continues to increase in Latin America, while the rates of diagnosis, treatment and control of these disorders remain low. The frequency of the risk factors that constitute the metabolic syndrome and are associated with an increased risk of cardiovascular disease has not diminished since the publication of the previous consensus. This document discusses the socioeconomic, demographic, environmental and cultural characteristics of most associated Latin American countries and partially explains the lack of better results in improving clinical and public health actions that allow high morbidity and mortality rates caused by cardiovascular diseases and DM2 to be reduced through programs aligned with the so-called precision medicine, which should be predictive, preventive, personalized and participatory. The Consensus ratifies the diagnostic criteria expressed in the previous consensus to define hypertension and DM2 but, for the metabolic syndrome, and in the absence of evidence, the recommendation is to implement a cohort study that determines the abdominal perimeter value associated with hard outcomes, such as DM2 and CVD. Meanwhile, we recommend modifying the criterion to more than 94 cm in men and more than 84 cm in women according to WHO recommendations. We also recommend the carrying out of a study that identifies the situation of hypertension and DM2 in people of African ancestry who, in Latin America, exceed 75 million and whose epidemiology does not include solid studies. With respect to the proposed therapeutic targets, we recommended maintaining those defined in the previous consensus, but insisting that early pharmacological management of prediabetes with metformin should be introduced, as should the treatment of diabetic hypertensive patients with a combination therapy of two fixed-dose antihypertensive drugs and management with statins. To increase adherence, the use of different drugs combined in a single pill (polypill) is recommended. The simplification of the therapeutic regimen is accompanied by greater control of cardiovascular risk factors, both in primary and secondary prevention, and has been shown to be cost-effective. The consensus recommends the use of the currently available polypill combining an angiotensin-converting enzyme inhibitor, a statin and aspirin for secondary cardiovascular prevention and in patients with a high cardiovascular risk, such as hypertension patients with DM2.

Keywords: hypertension, metabolic syndrome, type 2 diabetes mellitus

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; BP, blood pressure; CAMDI, Central American Diabetes Initiative; CCB, calcium channel blocker; CI, confidence interval; CVD, cardiovascular disease; DIU, diuretic; DM2, type 2 diabetes mellitus; DOTA, Declaration of the Americas on Diabetes; IDF, International Diabetes Federation; LASH, Latin American

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*Professor Zanchetti passed away in March 2018 before the Consensus document was finalized. His contribution was invaluable in setting priorities, interpreting the available evidence and establishing final recommendations. His advice will remain in our memories.

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Society of Hypertension; LATAM, Latin America; PAHO, Pan American Health Organization; PURE, The Prospective Urban Rural Epidemiology study; RAS, renin–angiotensin system; RCTs, randomized clinical trials; SLIM, Lifestyle Intervention on Postprandial Glucose Metabolism Study; SPC, single pill combination; UPF, ultra-processed foods; USA, United States of America

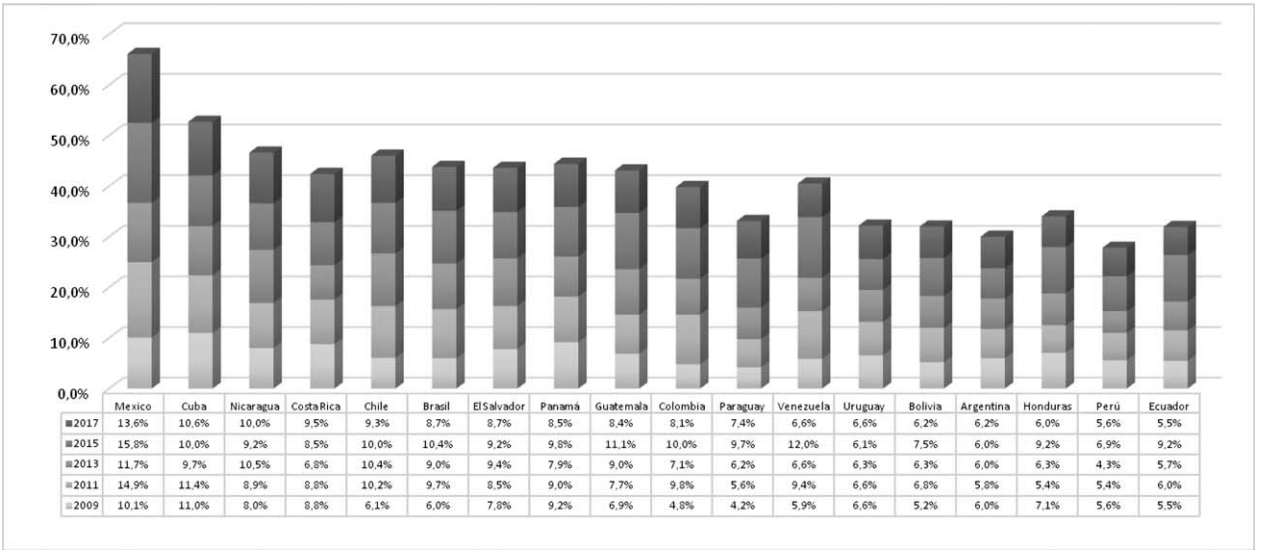
PREVALENCE OF HYPERTENSION, DIABETES MELLITUS AND METABOLIC SYNDROME IN LATIN AMERICA

In Latin America, hypertension is responsible for 1.6 million deaths annually because of cardiovascular disease (CVD) of which 500 000 occur before 70 years of age [1]. Hypertension is the main risk factor for coronary and cerebrovascular disease, affecting between 20 and 40% of Latin American adults [2–4]. Previous LASH guidelines and consensuses [5,6] described a high prevalence of hypertension and associated risk factors, as increasingly shown by reports from many countries [6]. However, the prevalence of hypertension differs widely between studies, which may be because of different definitions of hypertension, the age of the study populations, sampling biases, which are usually very small and the methods used to measure blood pressure (BP) [4]. The Prospective Urban Rural Epidemiology (PURE) study, carried out in four Latin American countries, is a population-based project that included people of both sexes aged 35–70 years, with 7497 people from Argentina, 5557 from Brazil, 3274 from Chile and 7478 from Colombia [7]. The prevalence of hypertension was 50.8% in Argentina, 52.6% in Brazil, 46.7% in Chile and 37.5% in Colombia: 57% of hypertensive patients were aware they were hypertensive, 52.8% had received treatment and only 18.3% were controlled (SBP <140 mmHg), rising to 36.3% in treated patients. Only 12.5% of hypertensive patients were receiving combination therapy with at least two antihypertensive drugs [8].

Recently, the results of a broadened sample of individuals from the PURE-LATAM study have been reported [9], including two studies with similar methodological characteristics carried out in Peru [10] and the countries of the Southern Cone of Latin America (Argentina, Chile and Uruguay) [11]. Table 1 shows the characteristics of individuals studied, in whom the global prevalence of hypertension was 44.6%, which was higher in Brazil (52.5%) and lower in Peru (19.3%): 59.6% of individuals knew they were hypertensive, which was higher in Brazil (64.8%) and lower in Colombia (51.9%), and 54.2% were receiving treatment, rising to 90.9% in persons who knew they were hypertensive, although only 37.6% were controlled (Table 1). Social inequality is one of the factors that most affects the control of hypertension, according to the PURE-Colombia study [12], which showed that the prevalence of hypertension was 37.5% in the study population, rising to 62.5% in persons with low educational levels. The study also found that the highest risk of uncontrolled hypertension occurred in overweight or obese men aged less than 50 years living in rural areas who had low educational and income levels [12]. These factors are also important in the rapidly accelerating increase in the prevalence of type 2 diabetes mellitus (DM2), which is observed globally and in Latin America.

TABLE 1. Hypertension awareness, treatment, and control in the population of Latin America by country and location

Country, region	Prevalence, *N* (%)	Aware, *N* (%)	Treated (among all with hypertension), *N* (%)	Treated (among aware), *N* (%)	Controlled (among all with hypertension), *N* (%)	Controlled among those receiving treatment, *N* (%)
Argentina						
Urban	3816 (50.5)	2249 (58.9)	2001 (52.4)	2001 (89)	679 (17.8)	679 (33.9)
Rural	1934 (49.6)	1024 (52.9)	974 (50.4)	974 (95.1)	273 (14.1)	273 (28)
Overall	5750 (50.2)	3273 (56.9)	2975 (51.7)	2975 (90.9)	952 (16.6)	952 (32)
Brazil						
Urban	2255 (53)	1447 (64.2)	1408 (62.4)	1408 (97.3)	532 (23.6)	532 (37.8)
Rural	662 (51)	442 (66.8)	422 (63.7)	422 (95.5)	152 (23)	152 (36)
Overall	2917 (52.5)	1889 (64.8)	1830 (62.7)	1830 (96.9)	684 (23.4)	684 (37.4)
Chile						
Urban	2098 (46.6)	1330 (63.4)	1151 (54.9)	1151 (86.5)	490 (23.4)	490 (42.6)
Rural	322 (45.7)	208 (64.6)	200 (62.1)	200 (96.2)	90 (28)	90 (45)
Overall	2420 (46.5)	1538 (63.6)	1351 (55.8)	1351 (87.8)	580 (24)	580 (42.9)
Colombia						
Urban	1391 (40.3)	782 (56.2)	726 (52.2)	726 (92.8)	298 (21.4)	298 (41)
Rural	1406 (35)	670 (47.7)	576 (41)	576 (86)	185 (13.2)	185 (32.1)
Overall	2797 (37.4)	1452 (51.9)	1302 (46.5)	1302 (89.7)	483 (17.3)	483 (37.1)
Peru						
Urban	505 (20.5)	337 (66.7)	286 (56.6)	286 (84.9)	170 (33.7)	170 (59.4)
Rural	73 (13.9)	18 (24.7)	9 (12.3)	9 (50)	7 (9.6)	7 (77.8)
Overall	578 (19.3)	355 (61.4)	295 (51)	295 (83.1)	177 (30.6)	177 (60)
Uruguay						
Urban	804 (51.6)	587 (73)	516 (64.2)	516 (87.9)	234 (29.1)	234 (45.3)
Overall						
Urban	10 869 (45.7)	6732 (61.9)	6088 (56)	6088 (90.4)	2403 (22.1)	2403 (39.5)
Rural	4397 (42.1)	2362 (53.7)	2181 (49.6)	2181 (92.3)	707 (16.1)	707 (32.4)
Overall	15 266 (44.6)	9094 (59.6)	8269 (54.2)	8269 (90.9)	3110 (20.4)	3110 (37.6)



	Mexico	Cuba	Nicaragua	CostaRica	Chile	Brasil	ElSalvador	Panamá	Guatemala	Colombia	Paraguay	Venezuela	Uruguay	Bolivia	Argentina	Honduras	Perú	Ecuador
2017	13,6%	10,6%	10,0%	9,5%	9,3%	8,7%	8,7%	8,5%	8,4%	8,1%	7,4%	6,6%	6,6%	6,2%	6,2%	6,0%	5,6%	5,5%
2015	15,8%	10,0%	9,2%	8,5%	10,0%	10,4%	9,2%	9,8%	11,1%	10,0%	9,7%	12,0%	6,1%	7,5%	6,0%	9,2%	6,9%	9,2%
2013	11,7%	9,7%	10,5%	6,8%	10,4%	9,0%	9,4%	7,9%	9,0%	7,1%	6,2%	6,6%	6,3%	6,3%	6,0%	6,3%	4,3%	5,7%
2011	14,9%	11,4%	8,9%	8,8%	10,2%	9,7%	8,5%	9,0%	7,7%	9,8%	5,6%	9,4%	6,6%	6,8%	5,8%	5,4%	5,4%	6,0%
2009	10,1%	11,0%	8,0%	8,8%	6,1%	6,0%	7,8%	9,2%	6,9%	4,8%	4,2%	5,9%	6,6%	5,2%	6,0%	7,1%	5,6%	5,5%

FIGURE 1 Prevalence of diabetes mellitus type 2 in Latin American countries according to the International Diabetes Federation, between 2009 and 2017. DM2, diabetes mellitus type 2.

The International Diabetes Federation (IDF) estimates that approximately 425 million people worldwide have DM2, of which one third are aged more than 65 years and 80% live in middle-income and low-income countries, and also estimates that the number will increase to 693 million by 2045 [13]. The prevalence of DM2 in Latin America ranges between 5.5 and 13.6% and has increased by between 3 and 12% between 2015 and 2017 in Argentina, Colombia, Costa Rica, Nicaragua and Uruguay (Fig. 1). The increase in the prevalence of DM2 also implies a significant increase in the disease burden for Latin American health systems. Thus, the risk of premature death in a patient with DM2 is higher than in those without DM2 [14] and the risk of cardiovascular death is double [15]. It is estimated that 40% of people with DM2 in Latin America are not diagnosed, making it difficult to accurately estimate the costs of managing DM2 and its complications for health systems [16,17].

As shown in Fig. 1, there are variations in the prevalence of DM2 between Latina American countries which, as happens in hypertension, may be because of the different diagnostic criteria used, the characteristics of the populations studied, the age groups evaluated and the diagnostic methods used. Migration to cities, greater access to screening and diagnostic tests, and environmental, social, cultural and economic factors that influence the demographic, epidemiological and nutritional transition, expressed as the aging of the population, changes in lifestyles (dietary habits and physical activity) and the increase in urbanization [18–20], are also influencing factors. All these factors contribute to the remarkable increase in overweight and obesity, particularly abdominal, seen in Latin America which, together with glycemic alterations, hypertension, dyslipidemia characterized by an increase in triglycerides and a decrease in HDL-cholesterol, are the components of the metabolic syndrome. The high prevalence of metabolic syndrome in Latin America described above [5] has been confirmed in a recent systematic review [21] and in new studies, such as the Central American Diabetes Initiative (CAMDI), sponsored by the Declaration of the Americas on Diabetes (DOTA) and the Pan American Health Organization (PAHO), which evaluated the prevalence of metabolic syndrome in Costa Rica (San José), Guatemala (Guatemala City), Honduras (Tegucigalpa), Nicaragua (Managua) and Belize, and reported a prevalence of metabolic syndrome of 30.3%, ranging from 23% in Honduras to 35.1% in Costa Rica. Nicaragua had the highest prevalence of hypertension (41.4%) and Guatemala the highest prevalence of hyperglycemia (28.2) [22].

Each metabolic syndrome component increases the risk of cardiovascular disease and all-cause mortality. However, the metabolic syndrome cluster increases the risk more than the sum of each independent component and is associated with a 1.5–2.5 increase in all-cause death, cardiovascular death and death because of DM2 [23,24].

DEFINITION OF OVERWEIGHT, OBESITY AND METABOLIC SYNDROME IN LATIN AMERICA

The concept that metabolic syndrome in Latin America should consider the criterion of abdominal obesity as mandatory is based on observations from recent studies that show the incidence and prevalence of overweight and obesity have increased progressively during the last six decades and alarmingly so in the last 20 years, reaching figures of 10–20% in childhood, 30–40% in adolescence and 60–70% in adults [25,26]. Due to the fact that Mexico has Official Mexican Standards on hypertension and overweight [27,28] which are mandatory, while the guidelines of the scientific society are only suggestions on the way to approach and treat a particular problem taking into account the characteristics of the patient, in order to unify criteria for Latin America, the Consensus recommends accepting the definitions of overweight and obesity determined by law in Mexico. Consequently, we define overweight as a BMI at

least 25 kg/m^2 and less than 29.9 kg/m^2 and in adults of short stature, at least 23 kg/m^2 and less than 25 kg/m^2. In persons aged less than 19 years, overweight is defined as a BMI between the 85th and 95th percentile of the WHO age and sex tables. Obesity in adults is defined as a BMI at least 30 and 25 kg/m^2 in persons of short stature. In persons aged less than 19 years, obesity is defined as a BMI in the 95th percentile of the WHO BMI tables for age and sex. Low stature is defined as less than 1.50 m in adult women and less than 1.60 m in adult men [27,28].

With respect to central obesity, a mandatory criterion for the diagnosis of metabolic syndrome, the current Consensus demands that the cut-off points to be proposed must be supported by a demonstration of therapeutic benefit or association with risk. Concerning therapeutic benefits, these should come from results of randomized clinical trials (RCT) or analysis of subgroups of RCTs showing a better prognosis after treatment in Latin American patients when dealing with a certain limit of the risk factor (glycemia, BMI, definition of metabolic syndrome, abdominal perimeter). Unfortunately, this evidence was nonexistent in the Latin American population with only few cohort studies that show associations between levels of these risk factors and the incidence of cardiovascular events or the presence of another risk factor, and no studies with an estimated event risk based on a Framingham-type risk scale. The most common studies are cross-sectional or case–control, in which the risk is estimated by the presence of CVD or by risk equations. Therefore, it is difficult to make a recommendation on the cut-off points to be applied to the Latin American population, and even more so when the characteristics of the Latin American population are considered, such as differences and ethnic mixes with variable proportions of European ancestors and the native population and, in some countries, with a black or Asian population [29–37].

The measurements proposed to define central obesity are waist circumference, waist/hip ratio and waist/height ratio. In general, there is a consensus that these measurements are more closely associated with cardiovascular risk than with BMI. Indexes that correct the waist perimeter per the hip circumference (waist/hip ratio) tend to have a better correlation and predictive capacity for DM2 or CVD than the waist circumference alone, although in some reports the benefit of adding these measurements is marginal. Therefore, the Consensus recommends the use of the abdominal perimeter, with the measurement being made at the midpoint between the palpable lower margin of the last rib and the upper edge of the iliac crest, at the end of expiration, with a nonelastic tape with a tension of 100 g [38].

In the absence of Latin American studies that met the quality criteria demanded, the previous Consensus [5] followed the IDF recommendations for South and Central American ethnic groups of at least 90 cm in men and at least 80 cm in women [39]. The present consensus also considered the WHO recommendations of more than 94 cm in men and more than 80 cm in women at increased risk, and more than 102 cm in men and more than 88 cm in women at substantially increased risk [40,41]. In the absence of evidence, the recommendation of the Consensus is to carry out a cohort study to determine the value of the abdominal perimeter best associated with hard outcomes, such as DM2 and CVD. Meanwhile, we recommend modifying the criterion to more than 94 cm in men and more than 84 cm in women, according to the WHO recommendations [40,41].

DIAGNOSIS AND CLASSIFICATION OF HYPERTENSION AND BLOOD PRESSURE TARGETS TO BE ACHIEVED IN PATIENTS WITH METABOLIC SYNDROME AND DIABETES MELLITUS 2

The consensus confirms the previous concepts [5,6,42] that hypertension is diagnosed in patients with metabolic syndrome and DM2 when office BP is measured at two different times and, according to the norms that validate the measurement [5,6], is at least 140/90 mmHg. We also maintain the classification of hypertension grade 1 as BP values between 140/90 and 159/99 mmHg; grade 2 as between 160/100 and 179/109 mmHg and grade 3 as at least 180/110 mmHg. Pharmacological treatment should be initiated when BP is more than 140/90 mmHg and, despite the debate about the BP targets that should be achieved, the current Consensus recommends reaching and maintaining values of less than 140/85 mmHg, considering that the optimal goal for SBP is 130 mmHg or less, and there is no additional benefit in trying to reach levels less than 120 mmHg, and the optimal goal for DBP is 80 mmHg, recommendations that coincide with the recent guidelines of the European Society of Cardiology/European Society of Hypertension [43].

DEFINITION OF THE DIAGNOSTIC CRITERIA FOR TYPE 2 DIABETES IN LATIN AMERICA

The diagnosis of DM2 is based on increased levels of glycemia and/or glycosylated hemoglobin (HbA1c). As these measurements are the only means to diagnose DM2, they must be adapted to each population according to genetic and epigenetic characteristics, which may vary in populations subjected to different socioeconomic conditions [44]. The WHO determined the cut-off points for glycemia and HbA1c for the diagnosis of DM2 based on the results of epidemiological studies conducted in high-income countries and which are associated with the risk of retinopathy [45,46], cut-off points that could be inadequate for medium-income and low-income countries, especially considering the association of these cut-off points with the risk of CVD [47,48]. The Consensus recommends the continued use of the WHO criteria for the diagnosis of DM2, which means meeting any of the following four criteria: criterion 1, symptoms of hyperglycemia, such as polyuria, polydipsia, polyphagia and unexplained weight loss, together with casual blood glucose at least 200 mg/dl, defining as casual the result obtained at any time of the day; criterion 2, glycemia at least 200 mg/dl 2 h after an oral glucose load. The test should be carried out as described by the WHO, using a glucose drink containing the equivalent of 75 g of glucose dissolved in water; criterion 3, fasting blood glucose at least 126 mg/dl and criterion 4, HbA1c at least 6.5%.

On the basis of the two works recently published in Latin America [49,50], the Consensus also recommends diagnosing and treating prediabetes, also known as glycemia with an increased risk of DM2, or intermediate hyperglycemia, a term proposed by the WHO referring to an intermediate metabolic state between normal glucose homeostasis and DM2 [45]. It is diagnosed by venous blood glucose levels: altered fasting blood glucose when values are between 100 and 125 mg/dl after at least 8 h of fasting, and/or glucose intolerance when glycemia values 2 h after the administration of an oral overload of 75 g of glucose are between 140 and 199 mg/dl, and/or if HbA1c values are between 5.7 and 6.4% [51]. According to the IDF, the worldwide prevalence of prediabetes varies between 6 and 14% and, for Colombia, the age-adjusted estimate (20–79 years) is 8–10% [52]. There is a large body of evidence showing that prediabetes progresses to DM2 at an annual rate of at least 10% and that, regardless of progression to DM2, it is a risk factor for cardiovascular disease [53–59]. Therefore, the Consensus recommends immediate management through changes in lifestyle and new assessments at 3 and 6 months once prediabetes is detected and diagnosed. If the patient does not respond with a weight loss of at least 5% and if HbA1C values are not normalized, pharmacological treatment with a dose of 500 mg/day of metformin should be initiated, escalating to 1500–1700 mg/day, according to tolerance.

SOCIOECONOMIC, ETHNIC, NUTRITIONAL AND GEOGRAPHICAL CHARACTERISTICS ASSOCIATED WITH THE RISK OF HYPERTENSION, METABOLIC SYNDROME AND DIABETES MELLITUS 2

Social risk

Latin America has a series of ethnic, economic, geographic and cultural characteristics that influence the high prevalence of hypertension, metabolic syndrome and DM2 [60]. Socioeconomic inequalities, which are common in Latin America [61] and which vary according to the ethnic composition, should be considered as a conditional risk factor for CVD which, in turn, contributes to an increased social risk [62]. Inequalities in social, economic and educational conditions contribute to chronic psychosocial stress, which is a frequent risk factor in the Latin American population, and which is associated with hypertension [12,63], DM2 [44], metabolic syndrome [64,65] and CVD [66–68]. Socioeconomic inequalities and differences in access to health services between urban and rural areas in Latin America are other determinants of the differences in the prevalence of CVD risk factors and their management [68–70]. Social inequalities are so characteristic of Latin America that the Latin American hypertension guidelines were the first to include social risk as a scoring factor within the risk scale of hypertension management [71]. Figure 2 shows the components of social risk and their association with hypertension, metabolic syndrome and DM2. Factors, such as the educational level, the income level, the possession or absence of housing and whether people have permanent jobs are conditioning factors of social risk, which is directly associated with access to healthy foods and the intake of macronutrients and micronutrients. The recent results of the PURE study have shown that low-income and middle-income countries, which include the Latin American countries participating in the study, have less availability, less access to and lower consumption of fruits and vegetables [72,73], proteins and fats [74], and milk and derivatives [75] compared with high-income countries. However, the consumption of carbohydrates, especially processed and ultra-processed ones, is greater [74]. These dietary characteristics, observed throughout Latin America, and particularly in the poorer socioeconomic sectors, are a risk factor for hypertension, dyslipidemia, obesity and CVD [76,77].

Mass internal migration from the countryside to the big cities, seeking, at least in theory, greater opportunities, has led to an accelerated, disorganized process of urbanization, which is another characteristic aspect of Latin America related to poverty, with social inequities and, in some countries, situations of forced displacement because of political violence. This migration results in the formation of marginal suburbs lacking any health infrastructure, and changes in lifestyles with the adoption of unhealthy habits, such as the consumption of processed foods and sedentary lifestyles [78,79]. The Chronicles study in Peru [64] found a difference in the prevalence of obesity among rural inhabitants, migrants from rural areas to urban areas and urban dwellers. The prevalence of obesity was 3, 20 and 33%, respectively, and the prevalence of DM2 0.8, 3 and 6%, respectively.

Education and schooling are also key determinants of the risk of hypertension, DM2 and obesity [80]. The PURE-Colombia study found that, in men aged less than 50 years with lower salaries living in rural areas, the lower level of schooling was the factor that most influenced not only high BP but also the treatment and control of hypertension [12]. In Latin America, dropping out of school is common because of the economic conditions of households, which further aggravates the already-low number of individuals from lower social classes who have access to primary education and almost no possibility of accessing higher education [81]. This, in turn, is related to an increase in risk factors [80] and cardiovascular events [82], an association consistent with that found in other populations [83].

Ethnic and geographical factors

Another characteristic of the Latin American population is the enormous degree of mixing between ethnic groups, from Indian aborigines through the European whites and blacks of African ancestry and, more recently, large migratory groups of Asians and Syrian-Lebanese, which has contributed to the mixture of ethnicities that makes the definition and categorization of ethnic groups difficult [5,84]. However, the black skin characteristic of African ancestry, the greater risk of developing hypertension and DM2, and the large black population in Latin America, determined that the previous consensus [5] concluded that, before 2012, there was no large epidemiological study on the prevalence of hypertension and diabetes in this population, and that no study with a representative sample has

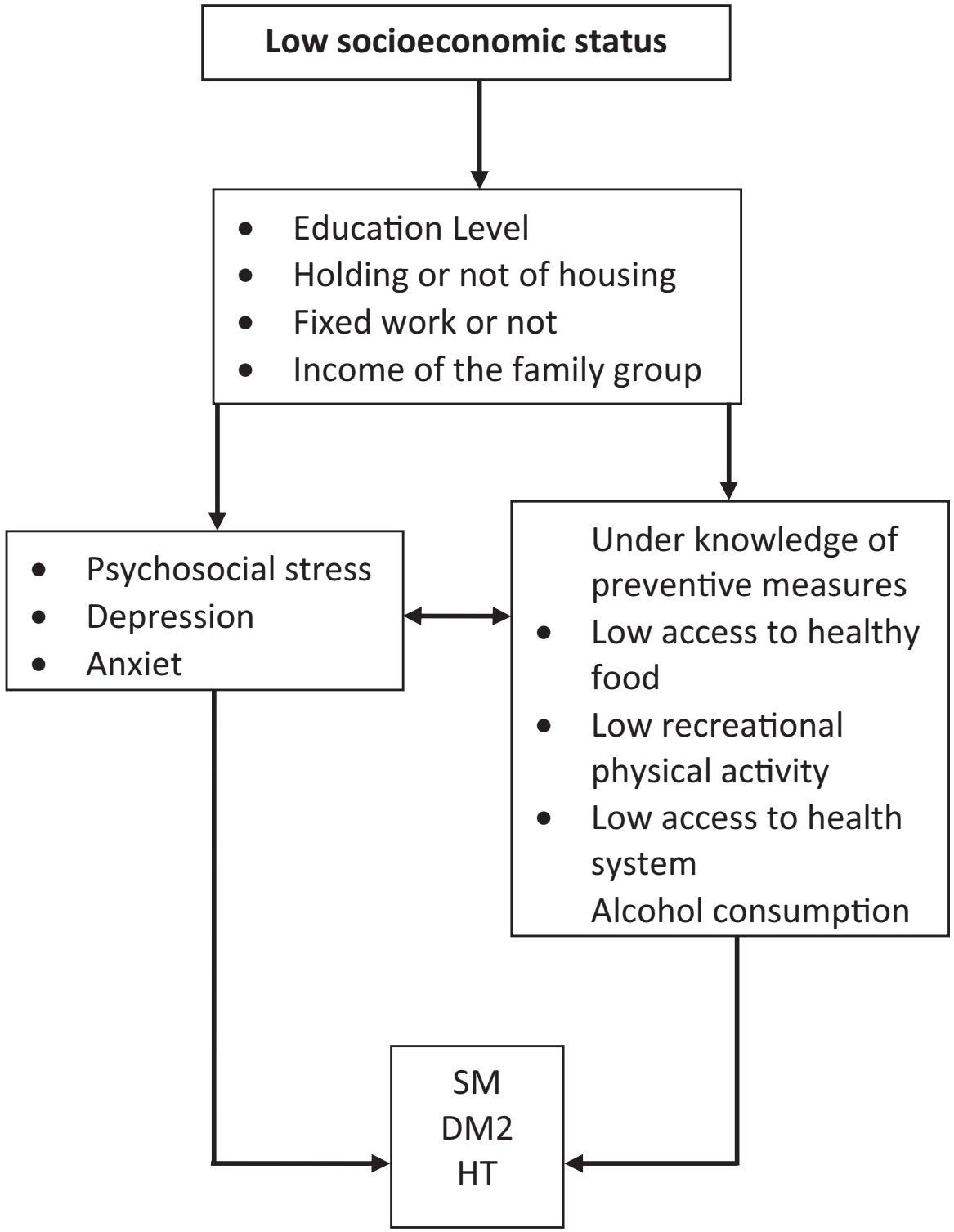


FIGURE 2 Factors involved in social risk and its consequences.

investigated food intake, physical activity and body composition, factors associated with hypertension and diabetes in this group. It, therefore, recommended carrying out epidemiological, clinical and therapeutic research in persons of African ancestry living in Latin America to verify whether the results of US studies are applicable to the black population of Latin America. In addition, it was recommended that, until there was an adequate amount of data from studies in the black population of Latin America, the adoption of the guidelines of the International Society of Hypertension in Blacks, a document that highlights the high prevalence of the coexistence of hypertension with obesity

and DM2, especially in women, as well as the greater frequency of cardio-renal complications associated with hypertension and DM2 [85]. In spite of the recommendation to conduct new epidemiological studies in this region, very few studies in Latin American people of African ancestry have been published between 2012 and 2018 [86,87], and those have found a higher prevalence of hypertension and lower rates of diagnosis, treatment and control of hypertension with respect to other ethnic groups. Most studies from the Caribbean islands [88–94] show that blacks in the Caribbean have a higher prevalence of hypertension than whites in the United Kingdom and that, moreover, there is higher mortality because of causes associated with hypertension than that presented by blacks in the United Kingdom, especially women. However, in the population of Cuba where there are no great differences in social risk between whites and blacks and where hypertensive patients had equal access to medications [95], it was shown that differences in BP levels were less pronounced, which underlines the fact that in addition to the proposed higher genetic sensitivity to sodium intake presented by people of African descent [96], other socioeconomic factors may be interacting to determine the higher prevalence of hypertension and DM2 observed in this specific population in Latin America [97]. The implication of clearly determining these factors is of great importance in the public health of the Latin American countries with a high percentage of blacks [84,98]. Therefore, this Consensus insists on recommending, to Latin American Science and Technology systems, the need to finance projects that clarify the causes of the greater risk in people of African ancestry of presenting a higher incidence of hypertension and DM2 (Table 2).

Altitude-induced hypobaric hypoxia involves adaptive changes in many physiological systems in exposed individuals and may have important effects on the regulation of BP and the glucose metabolism [99–102]. The population of Latin America living in the Andes Mountains shares similar characteristics and historical colonization patterns with people living at lower altitudes, being mostly Amerindians or mixed race. People living at high altitudes in the Andes (>3000 m above sea level) constitute a special group in whom the prevalence of hypertension and diabetes is poorly understood. However, the few existing data suggest there are no differences in the prevalence of hypertension and DM2 between them and populations living at sea level or lower altitudes, as reported in the previous consensus [5]. Recently, a higher prevalence of hypertension has been described in Colombian populations living at sea level (44.8%) than in those living at altitude (>2000 m above sea level: 36.0%) [12]. However, this study could not exclude the influence of the ethnic group because it is well known that the percentage of black people living at sea level is greater than that of those living at high altitude. In addition, altitude is related to greater exposure to cold, which increases BP levels, as has been demonstrated in other populations [103–105]. The lack of data led to the previous consensus recommending the initiation of studies to define the role of altitude and concomitant low temperatures in the risk of hypertension in Latin America. Parati *et al.* have initiated a series of studies in Peru, Ecuador and Colombia with the aim of defining, in the high Andean population, whether the prevalence of hypertension differs from that of people living at sea level, and of determining the mechanisms involved and their impact on the management of hypertension in these Andean high-altitude populations [106,107].

Food characteristics

Noncommunicable chronic diseases are attributed to inadequate human behavior, especially that related to diet,

TABLE 2. Ethnic groups in different areas of Latin America

Country	Mixed race (%)	White (%)	Indigenous (%)	Black (%)	Total population	Black population
Haiti	0	5	0	95	10 994 000	10 444 300
Belize	48.7	4.6	10.6	36.1	369 000	133 209
Cuba	14.9	64.1	0	20	11 252 000	2 250 400
Brazil	33.1	47.7	0.3	19.7	204 519 000	40 290 243
Panama	70	10	6	14	3 764 000	526 960
Costa Rica	3.6	80.8	2.4	13.2	4 851 000	640 332
Puerto Rico	8.5	75.8	3.3	12.4	3 508 000	434 992
Dominican Republic	73	16	0	11	9 980 000	1 097 800
Colombia	49	37	3.4	10.7	49 987 000	5 348 609
Nicaragua	69	17	5	9	6 459 000	581 310
Ecuador	79.3	6.1	7	7.6	16 279 000	1 237 204
Venezuela	49.9	42.2	2.7	4.6	30 620 000	1 408 520
Uruguay	8	88	0	4	3 310 000	132,400
Peru	37	15	45	3	31 153 000	934 590
Honduras	90	1	7	2	8 950 000	179 000
Bolivia	32	12	54	2	10 520 000	210 400
Paraguay	75	20	3	2	7 003 000	140 060
Argentina	10	86	3	1	43 132 000	431 320
Mexico	75	15	9	1	121 006 000	1 210 060
Guatemala	41.7	18.5	39.8	0.4	16 176 000	64 704
Chile	44	52	4	0	18 006 000	0
El Salvador	86.3	12.7	1	0	6 514 000	0
Mean/total	45.4	33	9.4	12.2	618 352 000	75 523 265

physical activity, smoking and alcohol. Guidelines and consensuses on hypertension, diabetes, overweight, obesity, dyslipidemia and atherosclerotic disease agree that lifestyle modifications are the preferred first-step intervention for the prevention or treatment of these conditions, either when they occur in isolation or when they do so in various ways, as happens in metabolic syndrome . Any strategy that tries to influence these risk factors is expensive as it requires a complex approach and highly qualified professionals, making these interventions not affordable for low-income and middle-income countries, where illnesses derived from unhealthy lifestyles are the most prevalent.

In 2014, the NutriCoDE study, designed and directed by the Global Burden of Diseases Nutrition and Chronic Diseases Expert Group [108] systematically studied and analyzed 266 national adult nutrition surveys, evaluating the consumption of saturated fats, fatty acids Ω-6 and Ω-3 from fish, fatty acid Ω-3 from plants, trans fats and dietary cholesterol. The study showed that, in Latin America, there is a high level of cholesterol and trans fats in the regular daily diet. In Mexico, the consumption of cholesterol and trans fats can be as high as 4.5 g/day. Saturated fats are consumed in a similar pattern to that which occurs in other areas of the developing world comparable with Latin America, but unsaturated fatty acids are consumed in significantly smaller quantities, especially with respect to the low consumption of Ω-3 from marine fish sources. In countries, such as Bolivia, Paraguay, Argentina, Mexico and the Dominican Republic, the consumption is less than 50 g/day. This situation, which may be understood in Bolivia and Paraguay, countries without an oceanic coast, cannot be explained by this reason in the other countries mentioned, all of which have long coastlines, including the Dominican Republic, which is an island. Therefore, this imbalance in the consumption of polyunsaturated fats from fish is a consequence of cultural, economic and educational situations, which affords an opportunity to intervene in the population through education and laws that limit the consumption of trans fats, given that the largest sources of these fats are fried flours containing margarine. In addition, the high consumption of refined sugars, soft drinks with added sugar and ultra-processed foods (UPF) in ready-to-eat or drink formulations, which contain more sugar, more trans fats and more sodium, are widely consumed in Latin America, as they are accessible, practical, ubiquitous, very well publicized, tasty and highly addictive [109]. UPF consumption is associated with an increase in adult BMI at all levels of consumption, after adjustment for covariates ($R^2 = 0.79$, $P < 0.0001$), to the point that the per capita sale of these products (in kg) is an independent predictor of the increase in BMI over time [110]. The Pan American Health Organization (PAHO) conducted a study to estimate UPF consumption trends using sales information from the Euromonitor International 2014 database [111], and found that, in a time series analysis using national surveys from 12 countries between 1999 and 2013, which analyzed the association between changes in annual sales per capita of UPF (in kg) and changes in the mean standardized BMI in adults, the Latin American market is the third in the world, behind Asia and Canada, with an increase of 50% in consumption between 2000 and 2013, surpassing the US market in the sale of sugary soft drinks in 2013. The five countries with the highest consumption of UPF per capita are Mexico, Argentina, Chile, Bolivia and Paraguay which, in turn, are the five countries with the highest BMI and the highest incidence of obesity.

Dietary recommendations

Most studies have found that the gold-standard or first-line indication with respect to cardioprotective diets is the Mediterranean diet, which demonstrated effectiveness in longitudinal studies and can be recommended both in primary and secondary prevention of cardiometabolic diseases [112–115]. The Mediterranean diet is a cardio-protective diet, defined as 'foods and beverages that were consumed in the countries that border the Mediterranean Sea in the 1960s.' It is rich in unsaturated fats (olive oil, nuts, seeds), low in saturated fats (red meat), whole milk) and, in general, contains more fresh or natural foods (fruits, vegetables, whole grains) than processed foods. Saturated fats found in greater amounts in red meat, cheese, and whole milk increase total cholesterol and low-density lipoprotein (LDL)-cholesterol. For a long time, the intake of saturated fat, especially of animal origin, was considered the most important risk factor for cardiometabolic disease and low fat consumption was promoted at the expense of saturated fats. Recently, the PURE study established that this recommendation caused high consumption of processed carbohydrates in order to cover calorific requirements, resulting in excess consumption that increases the risk of cardiometabolic disease [74,76], whereas the adequate consumption of fats, similar to that of the Mediterranean diet, was associated with a significant reduction of 23% in total mortality risk, an 18% lower risk of stroke and a 30% lower risk of noncardiovascular mortality. Each type of fat was associated with a significant reduction in mortality risk: a reduction of 14% with saturated fats, 19% with monounsaturated fats and 20% with polyunsaturated fats. A higher intake of saturated fat was also associated with a 21% decrease in the risk of stroke (Table 3). Another important change in the dietary recommendations is the elimination of the restriction on the consumption of cholesterol of 300 mg/day as a strategy for the prevention of atherosclerotic disease. Since 2015, the warning on restricting foods with high cholesterol content, such as eggs, some meats or whole milk products, among others, has been eliminated [77].

This new evidence leads us to recommend a complete diet, that is, it must cover, in a balanced fashion, all dietary

TABLE 3. Consumption of macronutrients in South America and relationship with the risk of cardiovascular disease

Macronutrient	Percentage of energy derived from its consumption, mean (SD)	RR 95% CI
Carbohydrates	52.4 (11–3)	1.09 (1–2)
Total fats	25.2 (7–7)	0.95 (0.84–1.07)
Saturated fats	10.9 (3–7)	NA
Polyunsaturated	4.4 (1–6)	NA
Monounsaturated	9 (3–2)	NA
Proteins	17.5 (3–8)	0.96 (0.84–1.10)

Data from the PURE study [74]. NA, data not available; SD, standard deviation.

nutrients, be isocaloric, with 50–55% of energy ingested from carbohydrates, preferably from slowly absorbed natural carbohydrates, and must restrict the consumption of processed carbohydrates with a high glycemic index, maintain an adequate protein intake corresponding to 20–25% of the energy ingested, which the remaining 20–30% coming from fats, maintaining a 1–1–1 ratio between saturated, unsaturated and polyunsaturated fats. Currently, in the diet of most of the population of Latin America, this would entail avoiding processed foods with high calorific density, avoiding combining easily absorbed carbohydrates with fat, promoting the consumption of white meat over red meat and of foods rich in polyunsaturated fats (Ω-3) at least twice a week, such as fish and nuts, stimulating the consumption of legumes (100 g two or three times per week), including those originating in Latin America, such as quinoa and lupine (*Lupino mutabilis*), which are of high nutritional value and have been shown to be useful in the coadjuvant management of DM2 [77,116,117].

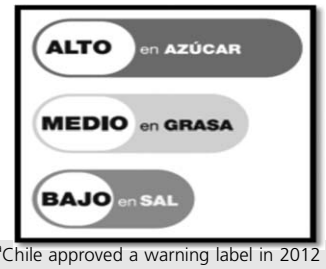
The consumption of natural foods offers a contribution of dietary fiber that is lost in industrial or home processed food. It is advisable to ingest the natural fruit, as the contribution of carbohydrates per gram (fructose) is lower than that of juice, which may contain more than twice that of fresh fruit. The PURE study also established that the recommendation to ingest five fruits/vegetables per day exceeds the daily carbohydrate requirements, suggesting an intake of three servings per day [73].

We emphatically and repeatedly recommend minimizing the intake of sweetened beverages, as these are very important risk factors for the Latin American population, especially children, and the intake of artificial beverages, such as soft drinks, instant tea or energy drinks. The consumption of sweeteners should be avoided, as this group of artificial additives, without calorific value, is sweeter than sugar, making it more difficult to wean patients from sweet foods. They have not shown significant benefits on health, and have recently been linked to an increase in BMI and DM2. Therefore, this Consensus does not recommend their consumption and promotes a reduction in simple sugars as the most appropriate way to reduce the calories derived from carbohydrates.

Another controversial issue in the dietary recommendations is related to salt consumption. Reports based on the results of the PURE study [118–122] confirm the positive association between sodium intake and SBP. This association is particularly evident in populations and individuals with a higher sodium intake (>5 g/day, equivalent to >12.5 g/day of salt), but not when sodium consumption is lower. Sodium intake was associated with a significant increase in stroke rates only in populations with salt intake in the upper tertile, and most were communities in China. Unexpectedly, there was an inverse association between sodium consumption and acute myocardial infarction (AMI) and mortality rates, while the increase in potassium consumption was associated with a significant decrease in all cardiovascular events. The magnitude of the association between sodium consumption and SBP (2.86 mmHg per 1 g increase in sodium consumption) was more robust than that reported in the INTERSALT (1.94 mmHg) [123] and INTERMAP (0.22 mmHg) studies [124]. However, this association only occurs in communities with a mean sodium consumption similar to that observed in China (5.58 g/day), and not in countries whose mean consumption is in the order of 4.49 g/day. These results have led some sectors to support them with data obtained in different populations [125–130], whereas others have questioned them [131,132]. The contrasting data suggest that the current recommendations for sodium intake [133,134] need to be re-evaluated [135] and that the impact of reductions in salt intake in reducing CVD should be the subject of controlled clinical studies, which are already being implemented [136]. This should allow the resolution of disputes that, as pointed out by Alberto Zanchetti, 'are welcome, because it is through controversy that science advances' [137]. Meanwhile, the recommendation to reduce sodium consumption as a measure preventive for hypertension and CVD should be, rather than a universal population intervention, directed and implemented in those communities and individuals in whom sodium consumption is more than 5 g/day, which will avoid the dispersion of resources in trying to introduce this measure in communities or individuals in whom the consumption of sodium is less than this amount and who will not benefit from the intervention. In addition, there is a risk that reducing sodium intake to minimum levels in populations that consume an adequate amount may increase the risk of AMI and death. On the other hand, the difficulty in ensuring good adherence to diets very restrictive in sodium is well known and, as was pointed out by Pickering [138] 'rigid low-sodium diets are tasteless, unappetizing, monotonous, unacceptable and intolerable. To maintain them requires the asceticism of a religious fanatic.'

Lifestyle modifications should be recommended in high-risk adults, such as patients with diabetes and hypertension, as an important complement in the control of their problems and in reducing medicament use. However, major efforts should focus primarily on the creation of healthy lifestyles in the expectant mother, during childhood and throughout life, as recommended by the Lancet Commission on Hypertension [139]. Recently, the concept of the first 1000 days has been gaining acceptance [140,141]. This includes a critical period that covers 40 weeks of gestation and the first 2 years of life, as the changes generated in this stage are decisive. It is considered to be a unique window of opportunity to shape and improve health in the short-term and long-term, given that it is a stage of cell formation, multiplication and differentiation from the pluripotent stem cell. Early feeding and metabolic programming influence genetic expression by modifying, among other things, the risk of chronic noncommunicable disease. In this stage of high plasticity and accommodation to the environment, it is important that the body receives all the nutrients needed for optimal development. Deficiencies and excesses can result in metabolic changes that could predispose to the appearance of noncommunicable diseases, such as cardiovascular and metabolic diseases, among others [19,78,142]. During the first 1000 days, the most important risk factors for cardiometabolic disease in children are: obese or overweight mother, excess maternal weight gain during pregnancy, maternal smoking, rapid weight gain in the first year of life and little or no contribution of breast milk.

TABLE 4. Food- labeling policies

Countries with mandatory policies	Countries with voluntary policies
Mexico: established the mandatory GDA system in all industrial products in July 2015. In addition, the health ministry established voluntary labelling to indicate whether one product is healthier than another in accordance with established criteria	CODEX ALIMENTARIUS: Argentina, Bolivia, Colombia, Ecuador, Peru, Dominican Republic
[a]Ecuador adopted the traffic light system in all industrial products in November 2015 	SIECA (Central American Integration Secretariat): Brazil, Chile, Colombia, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panama
[a]Chile approved a warning label in 2012 in products exceeding established nutritional limits 	MERCOSUR (Common Market of the South): Argentina, Bolivia, Brazil, Paraguay, Uruguay, Venezuela

[a]Defined nutritional criteria.

Therefore, the introduction of mass nutritional education programs for pregnant women and children and adolescents, in addition to adults with risk factors and CVD, is a priority as are new laws and actions aimed at reducing the consumption of these products, such as an increase in taxes. These strategies are recommended by the present Consensus, which also demands from medical-scientific societies, primary and secondary educational institutions, and universities, the establishment of programs to promote, advice, endorse and organize structured campaigns to create awareness in all social sectors, and especially in children and adolescents, the risk implied by excessive consumption of these products.

Laws on food labeling and health literacy

As mentioned above, in recent years, there has been a large increase in the sales of processed and ultra-processed foods in Latin America, including snacks and sugary drinks, a phenomenon related to the high rate of overweight and obesity. Between 1999 and 2013, sales of processed foods and sugary beverages increased hugely, mainly in countries, such as Chile and Mexico [143]. In fact, Chile is the main consumer of sugary drinks per capita in the world, followed by Mexico and the USA.

The link between processed food and obesity is well documented and begins in childhood [143]. The problem of childhood obesity requires a broad response that takes into consideration the current obesogenic environment in Latin America. In the context of the fight against obesity, a key component, which UNICEF supports in the countries of the region, is the regulation of the labeling of processed foods and beverages aimed at children and adolescents, which would contribute positively to reducing obesity levels in these age groups. [144–147].

There have been some innovative actions in Latin America, such as the taxing of soft drinks in Mexico, new food labeling in Chile and, in Brazil and Uruguay, the publication of food guidelines that adopt a food classification according to the degree of processing. Analysis of current food labeling regulations in Latin America and the Caribbean shows Chile, Ecuador and Mexico have introduced frontal labeling as a public health strategy. Food labeling is associated with several factors, such as the level of education and the type of diet (Table 4).

Frontal labeling is effective when displayed in a simple, consistent, eye-catching way that can be interpreted quickly. For this, it is proposed to direct the efforts of the regulation of frontal labeling at the most vulnerable groups (those with lower educational and socioeconomic levels and who live in rural areas, among others), and promote the introduction of frontal labeling of industrialized foods and beverages that is simple and striking, does not require mathematical skills, takes little time to interpret and is consistent throughout the region. The labeling must be supported by scientific evidence generated by institutions without conflicts of interest; it must include the different elements of food and beverage packaging, and must be accompanied by an educational campaign that ensures sustainability. It is important to develop these campaigns to improve understanding and use by consumers, especially parents and children. Civil society must provide information about the use and understanding of frontal labeling systems, and request and demand best practices.

Alcohol consumption

In Latin American countries, the mean annual per capita consumption of alcohol is 2.2 l, higher than the rest of the

world's regions [148]. The relationship between consumption more than 35 g/day and the risk of hypertension, metabolic syndrome, DM2 and CVD is well established [149,150]. The PURE study analyzed the data obtained in 12 of the participating countries in which alcohol consumption is allowed [150], and included 114 970 adults of whom 12 904 (11%) were from high-income countries, 24 408 (21%) from upper middle-income countries, 48 845 (43%) from low middle-income countries and 28 813 (25%) from low-income countries, with a mean follow-up of 4.3 years. Current drinking was reported by 36 030 (31%) people and was associated with a reduction in the risk of myocardial infarction [hazard ratio 0.76 (95% CI 0.63–0.93)] and an increase in types of cancer related to alcohol [hazard ratio 1.51 (95% CI 1.22–1.89)] and accidents [hazard ratio 1.29 (95% CI 1.04–1.61)]. High alcohol intake was associated with increased mortality [hazard ratio 1.31 (95% CI 1.04–1.66)]. There was a significant reduction in the hazard ratio for the composite of major CVD in high-income countries compared with people who never drank, but not in low-income and middle-income countries, which shows that alcohol consumption has different associations according to the socioeconomic status of the countries. On the basis of these data, we recommend introducing actions aimed at avoiding excess alcohol consumption in Latina American countries as a strategy to reduce the risk of hypertension and other risk factors for CVD, such as atherogenic dyslipidemia, which is extremely frequent in Latin America [151].

Physical activity

The increase in sedentary behavior due, in large part, to technological advances in transportation and entertainment is contributing to the increase in the rates of obesity, DM2, hypertension, CVD and all-cause mortality [152,153]. Although most studies have been conducted in high-income countries, the PURE study recently evaluated the effect of physical activity on mortality and cardiovascular disease in 130 000 people without cardiovascular disease from 17 countries classified as high, medium and low income, including Latin American countries, such as Argentina, Chile, Brazil and Colombia [154]. It was shown that the greater the physical activity, the lower the prevalence of hypertension and DM2. The reduction in the relative risk between groups with high physical activity compared with groups with low physical activity was 86% for hypertension and 66% for DM2. The reduction in the relative risk for total mortality and CVD was 28 and 20%, respectively. The lowest risk was presented by people who engage in high and moderate physical activity compared with those who engaged in low physical activity. High physical activity was defined as more than 750 min per week of moderately intense physical activity, moderate physical activity as 150–750 min per week and low physical activity as less than 150 min. The benefit was independent of whether the physical activity was recreational or not, or whether individuals came from high-income, medium-income or low-income countries, which shows the association is global.

Other studies in adults have shown that aerobic physical activity reduces SBP on average by between 2 and 5 mmHg and DBP between 1 and 4 mmHg, and it is estimated that the reduction in BP can explain up to 27% of the reduction in CVD rates associated with regular physical activity [155–157]. We accept that the greatest benefit on BP is obtained from moderate-to-vigorous aerobic exercise three to four times a week, with sessions of a mean of 40 min maintained for at least 12 weeks [157,158]. Multiple prospective studies have shown that physical activity can prevent or delay the onset of DM2 [159–161] and cardiovascular events [162–169].

Currently there is special interest in the role of skeletal muscle in DM2, as this tissue is one of those most involved in the use and storage of glucose, and it is well documented that the loss of muscle mass (sarcopenia) is associated with alterations in blood glucose and BP [170–172]. It has been shown that muscle strength and muscle mass play an important role in the cardiovascular outcomes of patients with hypertension and DM2. The ORIGIN study found a 1 kg increase in prehensile strength in prediabetic and diabetic patients was associated with a reduction of between 9 and 30% in total mortality and mortality from CVD, AMI and stroke [173]. The PURE study in more than 130 000 apparently healthy people showed that a reduction of 5 kg was associated with an increase of between 7 and 17% in the risk of cardiovascular mortality, all-cause mortality and mortality because of AMI and stroke, and that, in addition, loss of prehensile strength was as predictive of CVD as increased SBP [174]. This association between lower prehensile strength and cardiovascular risk factors occurs from childhood [175]. In support of the results of these epidemiological studies, studies have shown that resistance training, the most powerful stimulus for the development of muscular strength, reduces the incidence of DM2. The SLIM study [176,177] reported a reduction of 18% in the cumulative incidence of DM2 in the intervention group, which included access to a combination aerobic and resistance training program. Currently, there are no data on this intervention in the Latin American population, although a study in young Colombian adults with excess weight observed an improvement in insulin sensitivity in the group of individuals undergoing weight training [177].

In addition, it has been shown that in children, the greatest muscle strength is associated with lower BP levels [171], and in individuals with hypertension it has been shown that both aerobic training and strength training are well tolerated and effective in reducing BP, with mean reductions of 11/5 mmHg (systolic/diastolic) after moderate-to-high intensity training, and with minor but significant effects using dynamic strength training, whereas isometric activity results in a reduction in BP similar to or greater than that observed with aerobic training [178–181].

In low-income and middle-income countries where, because of fetal programming and nutritional deficiencies during the early stages of life, the PURE study showed a higher prevalence of lower muscle mass and strength, with clear regional and country differences that made it necessary to establish differentiated reference ranges [182]. Therefore, avoiding sarcopenia is essential, and we recommend an increase in strength training and protein intake, which can significantly reduce the loss of muscle mass during the negative energy balance. In addition, after high

protein diets, a decrease in HbA1c has been reported as has a trend to BP reduction in people with DM2, without adverse effects on blood lipids [183].

Environmental pollution

More than 90% of the world's population is exposed to pollution levels that exceed the WHO air quality guidelines, which recommend a level of good quality air environments of less than 10 $\mu g/m^3$ of particulate pollutants [184–186]. The Lancet Commission on Pollution and Health [187] and the Global Burden of Disease [188,189] estimate that diseases caused by all forms of pollution were responsible for 9 million deaths in 2015, more than those attributed to obesity, alcoholism, traffic accidents, child or maternal malnutrition, and of the combination of AIDS, tuberculosis and malaria, and being surpassed only by hypertension and the combination of all nutritional factors.

The most worrisome environmental pollutants are volatile organic compounds and nanoparticles less than 2.5 μm in diameter ($PM_{2.5}$). Recent calculations estimate that 3.15 million deaths per year are attributable to $PM_{2.5}$, which places environmental pollution among the top 10 risk factors for global mortality [187–189]. More than half the health burden of these particles is related to cardiovascular disease, and it has been shown that exposure to $PM_{2.5}$ increases the risk of AMI, hospitalizations and deaths because of heart failure, stroke and arrhythmias [190–194].

Inhalation of $PM_{2.5}$ can trigger acute elevations in BP over the subsequent hours or days, and long-term exposure can lead to an increase of 13% in the risk of new cases of hypertension [195–199]. $PM_{2.5}$ and other environmental pollutants can worsen insulin resistance and promote DM2 [200–202]. Although most studies have been conducted in high-income countries, there is evidence that the situation in Latin America is similar [202–208]. This information shows that, in addition to changes in diet and physical activity to prevent hypertension, DM2 and CVD, it is the responsibility of Latin American governments to take measures to reduce environmental pollution through environmental protection agencies.

Smoking

Smoking continues to be one of the main avoidable causes of morbidity and mortality, with almost six million deaths each year worldwide because of diseases associated with smoking [189]. The recent meeting of the Working Group of the European-Latin American Respiratory Diseases Society held in Madrid showed that Latin America is making progress in smoking control [209], but that it is still necessary to increase the strictness of antismoking laws, increase taxes on cigarettes and develop alternative packaging plans. In Latin America, the results of smoking control programs have been reported in recent years [210–226], with excellent results obtained in Uruguay, Brazil, Chile and Panama through actions, such as the prohibition of smoking in public places, the imposition of high taxes and the inclusion of large warnings on cigarette packages, all agreed with the active participation of the leaders of governments, including, in Uruguay, the direct participation of the President of the Republic. Unfortunately, the same does not occur in other countries of the region, such as Argentina, Peru, Guatemala, Honduras and Nicaragua. The PURE study analyzed this situation in 12 953 adults from countries that ratified the international reference framework for smoking control, and found that the implementation of control policies is weak, especially in the lower income countries, and that the possibilities of quitting smoking are greater when antismoking measure are effective, social acceptance of smoking is lower and knowledge of the health damage is greater [227]. The implementation of these actions throughout Latin America is crucial to combat the increase not only in the incidence of cancer and CVD, whose association with smoking is well described, but also of DM2, as demonstrated by a recent meta-analysis of 88 prospective studies that involved almost six million participants and 295 446 new cases of DM2. This study showed that, compared with those who never smoked, the increaser in relative risk was 37% in active smokers, 14% in ex-smokers and 22% in nonsmokers with passive exposure. In addition, it was shown that the relationship is dose-dependent and it is estimated that 11.7% of cases of DM2 in men and 2.4% in women were attributable to smoking, equivalent to 27.8 million cases of diabetes worldwide. There is no doubt that efforts to reduce smoking will have a significant effect on the global burden of DM2 [228], and that the weight gain associated with smoking cessation does not affect the benefits of reducing cardiovascular and all-cause mortality [229].

PHARMACOLOGICAL TREATMENT IN HYPERTENSIVE PATIENTS WITH METABOLIC SYNDROME AND TYPE 2 DIABETES

Metabolic syndrome alone does not justify pharmacological treatment, as it is not considered a disease, but an agglomeration of different risk factors. Therefore, it is necessary to treat each of its constituents separately but at the same time [230]. As already discussed in the previous points, weight reduction, increased regular physical activity, reduced alcohol intake, smoking cessation, moderation of sodium intake, increased potassium consumption through greater fruit and vegetable intake and an adequate balance in the consumption of macronutrients are some of the important lifestyle changes recommended. By modifying these factors, the response to pharmacological treatment is improved and overall cardiovascular risk is reduced. In patients with diabetes mellitus and metabolic syndrome , the initiation of early antihypertensive treatment and BP control improve the survival and prognosis of cardiometabolic diseases [231,232], reducing the residual risk. The benefit is even greater than that attributable to the benefit of reaching glycemic and metabolic goals [233]. Therefore, treatment should be started as soon as BP is greater than 140/90 mmHg [234] and the goals are to reach less than 140/90 mmHg, and as far as possible to achieve less than 130/80 mmHg [235,236], which is associated with a decrease in the risk of coronary heart disease, left ventricular hypertrophy, heart failure, cerebrovascular accidents and deterioration of renal function [237–243] (Table 5).

TABLE 5. Blood pressure targets recommended by international guidelines for patients with type 2 diabetes

	ASH/ISH 2014	JNC-8 2014	LASH 2017	ACC/AHA 2017	ESC/ESH 2018
BP targets for type 2 diabetes mellitus	<140/90	<140/90	130–140/<90	<130/80	<130/80

ACC, American College of Cardiology; AHA, American Heart Association; ASH, American Society of Hypertension; BP, blood pressure; ESC, European Society of Cardiology; ESH, European Society of Hypertension; ISH, International Society of Hypertension; JNC, Joint National Committee; LASH, Latin American Society of Hypertension.

On the basis of various clinical studies, the Consensus recommends starting with combination treatment in a single pill (SPC), with the drugs of choice in patients with diabetes or metabolic syndrome being renin–angiotensin system (RAS) blockers, either and angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB), combined with a calcium channel blocker (CCB) or a thiazide-like diuretic, such as indapamide at low doses (DIU). If this dual treatment fails, triple (RAS and CCB combined with DIU) or quadruple treatment should be used (Fig. 3). Numerous studies show that combined therapy with two pharmacological groups is required in 50–70% of patients to achieve the goals [244,245]. One aspect to be considered is the antihypertensive effect of some hypoglycemic drug groups, particularly sodium-glucose cotransporter inhibitors [246], and therefore, BP should be carefully monitored in patients already receiving antihypertensive therapy, who should eventually be prescribed these antihypertensive drugs to avoid the sum of the effects and severe symptomatic hypotension.

Very low awareness, treatment and control of hypertension in the population in general, and particularly, in patients with metabolic syndrome and DM2 [247,248] is a serious problem, as 95% do not have controlled BP even though the number of antihypertensive drugs used is higher in patients with DM2 and metabolic syndrome . The benefit of antihypertensive treatment in risk reduction is only achieved when it starts as soon as possible, and goals are reached quickly and are maintained lifelong, in order to avoid accelerating vascular damage [249]. In a critical reassessment of controlled and randomized studies of the effect of BP reduction in hypertensive patients, Zanchetti *et al*. showed the divergence between international medical societies in establishing a BP value that justify interventions and setting the goals that must be achieved to obtain a greater reduction in major cardiovascular outcomes [250]. However, it is clear that the earlier pharmacological intervention is implemented and the management of all risk factors is addressed, the easier it is to prevent or halt the pathogenic process leading to cardiovascular diseases [251].

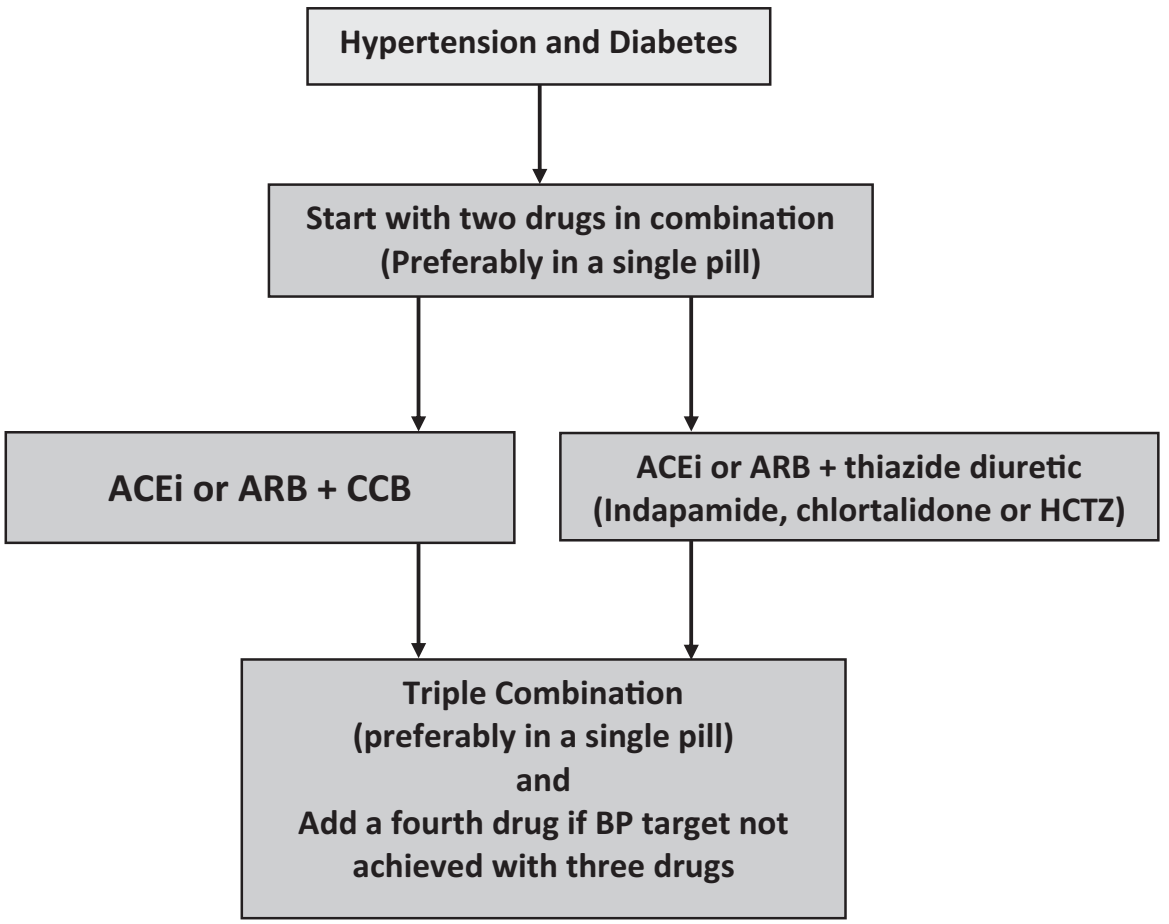


FIGURE 3 Antihypertensive treatment strategy recommended for diabetic patients with high blood pressure.

TABLE 6. Main causes of nonadherence to therapy

Health system	Bad physician-patient relationship Lack of access to medical care, lack of care continuity
Poor communication	
Condition	Chronic asymptomatic disease Mental health disorder (depression)
Patient	Physical deficits (visual problems, altered dexterity, cognitive deterioration, behavioral deterioration, psychological deterioration, age) Non-White ethnicity Nonattendance of medical visit
Therapy	Complexity of regime (multiple drugs)
Secondary effects	
Socioeconomic	Low literacy level Cost of drugs Poor social support

In addition, and considering that one in four hypertensive patients has DM2 [252,253] and that the administration of statins to these patients increases the prevention of cardiovascular events by almost double, as shown by the HOPE-3 study [254–256], the recommendation of this Consensus is to use two antihypertensive medications, a statin and metformin as initial treatment. However, although antihypertensive and hypoglycemic drugs are listed as essential medicines by the WHO [257], availability and access to them are limited in medium-income and low-income countries, as shown by the PURE study [258–261]. Although at least one antihypertensive drug was available in 90% of the pharmacies surveyed, the availability of two or more drugs was lower in medium-income and low-income countries and, given the economic conditions, access was also low because of the high costs relative to the low ability to pay of most households in these countries. As with hypertension, many people with DM2 remain unidentified, untreated or inadequately treated, especially in the lowest income countries, despite the existence of easy screening tests and effective medications [262]. The availability of and access to essential medicines to treat DM2 was very low in poor countries, both in terms of availability in pharmacies and the unattainable costs for the large majority. Thus, metformin was available in 100% and insulin in 94% of pharmacies in high-income countries, but only in 65 and 10%, respectively, of pharmacies in low-income countries. Although only 0.7% of households with diabetic patients in high-income countries cannot afford to buy metformin, this rises to 26.9% in poor countries. Access is even worse for insulin, with 63% of households in poor countries unable to buy it.

Therefore, in order to improve the control of hypertension and DM2, it is essential that Latin American health systems guarantee availability and access to a core group of basic medicines, and that standardized treatment algorithms should be introduced, as previously proposed by LASH [244,245] and the WHO/PAHO [263–267]. This strategy is currently being piloted within the HEARTS program in Barbados, Cuba, Colombia and Chile [268], based on the positive experience obtained in other programs [269,270].

THE POLYPILL: A STRATEGY TO IMPROVE THE ADHERENCE AND CONTROL OF HYPERTENSION AND CARDIOVASCULAR EVENTS

Adherence to long-term treatment is defined as the degree of adherence to pharmacological treatment, and following a diet and/or the adoption of lifestyle changes that correspond to the recommendations agreed with the physician or other health professionals. Many reasons why patients abandon treatment have been evaluated. Table 6 shows the main causes of nonadherence to prescribed treatments [271].

The use of polypharmacy and the dosing frequency is one of the factors that most influence treatment abandonment, and it has been shown that patients are more adherent to treatment if they take a single tablet instead of several a day [272]. Among the different strategies proposed to increase adherence, combination of different basic drugs in

TABLE 7. Summary of the main recommendations of the Latin American Consensus

Hypertension
Maintain the classification of hypertension grade 1 as BP values between 140/90 and 159/99 mmHg; grade 2 as between 160/100 and 179/109 mmHg and grade 3 as at least 180/110 mmHg
Pharmacological treatment should be initiated when BP is more than 140/90 mmHg, reaching and maintaining values of less than 140/85 mmHg and less than 130/80 mmHg if tolerated
Start treatment with a combination of two antihypertensive drugs in a single pill (SPC)
Avoiding excess alcohol consumption and smoking
Consume a healthy diet, that must cover in a balanced fashion all dietary nutrients, being isocaloric, with 50–55% of energy ingested from carbohydrates, 20–25 proteins, which the remaining 20–30% coming from fats, maintaining a 1–1–1 ratio between saturated, unsaturated and polyunsaturated fats
Increase physical activity and avoid sarcopenia by increasing strength training and protein intake, which can significantly reduce the loss of muscle mass
Overweight, obesity, the metabolic syndrome and type 2 diabetes
To carry out a cohort study to determine the value of the abdominal perimeter best associated with hard outcomes, such as DM2 and CVD. Meanwhile, use the criterion of more than 94 cm in men and more than 84 cm in women
Accept the definitions of overweight and obesity determined by law in Mexico
Diagnose and treat prediabetes. Pharmacological treatment with a dose of 500 mg/day of metformin should be initiated, escalating to 1500–1700 mg/day
Establishment of programs to promote, advise, endorse and organize structured campaigns to create awareness in all social sectors, and especially in children and adolescents, the risk implied by the consumption of sweetened beverages
In patients with metabolic syndrome, treat each of its constituents separately but at the same time
Continue using the WHO criteria for the diagnosis of DM2
To carry out research projects clarifying the causes of the greater risk in people of African ancestry of presenting a higher incidence of hypertension and DM2
Implementation of the use of the polypill to improve adherence in secondary cardiovascular prevention and in high-risk cardiovascular patients, such as patients with metabolic syndrome, HTA and DM2
Recommend to the Latin American governments take measures to reduce environmental pollution

BP, blood pressure; DM2, diabetes mellitus type 2; CVD, cardiovascular disease; HTA, Health Technology Assessment; SPC, single pill combination.

a single pill (polypill) to treat different risk cardiovascular factors (hypertension and dyslipidemia) makes the patient much more adherent to medical treatment than when they must take several a day. The simplification of the therapeutic regimen is accompanied by better results in terms of therapeutic adherence and, as a consequence, a greater control of cardiovascular risk factors, both in primary prevention [273,274] and in secondary prevention [275], and has been shown to be cost effective [276]. The only available polypill in Latin America providing careful in-vitro and in-vivo studies which have shown the safety, tolerability and bioequivalence of all its components with the drugs given separately combine ramipril, atorvastatin and aspirine [277]. This polypill was obtained by research conducted in Spain from the Centro Nacional de Investigationes Cardiovasculares (CNIC) in collaboration with Ferrer International, and approved in 2014 by the European Medical Agency for use in secondary prevention of cardiovascular events in adult patients. Considering all these reasons, the Consensus recommends the use of the currently available polypill containing ramipril, atorvastatin and aspirin for patients in secondary cardiovascular prevention and in high-risk cardiovascular patients with indication of aspirin in the therapeutic regimen, such as patients with hypertension and DM2 (Table 7).

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Conflicts of interest

There are no conflicts of interest.

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Unintended positive and negative effects of drugs on lipoproteins

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Purpose of review
Dyslipidaemia is an important cardiovascular disease risk factor. Many drugs affect lipid profile and lipoprotein metabolism. We reviewed unintended effects of nonlipid modifying, commonly used medications on lipid profile and lipoprotein metabolism.

Recent finding
Several detrimental effects of many drug classes such as diuretics, antidepressant, anticonvulsant and antiretroviral drugs have been reported, whereas other drug classes such as antiobesity, alpha 1-blockers, oestrogens and thyroid replacement therapy were associated with positive effects.

Summary
Dyslipidaemia is a common side-effect of many medications. This should be taken into consideration, especially in patients at high risk of cardiovascular disease. Other drugs demonstrated positive effects on circulating lipids and lipoproteins. The impact of these unintended effects on atherosclerotic disease risk and progression is unclear.

Keywords
cardiovascular risk, circulating lipoproteins, drugs, lipoprotein metabolism, unintended positive and negative effects

INTRODUCTION

Statins and other lipid-modifying drugs are commonly used in clinical practice. Many other drugs have, however, unintended positive and negative effects on lipoproteins. In this article, we review and summarize unintended effects of pharmacological agents, in particular, nonlipid-modifying drugs, on lipoproteins.

CARDIOVASCULAR DRUGS

Cardiovascular drugs are commonly used in clinical practice and many of these agents can affect circulating lipoproteins [1–9]. In a meta-analysis of 474 studies including 65 000 patients on antihypertensive medications, Kasiske *et al.* [10] concluded that almost all antihypertensive medications, except calcium antagonists, affect serum lipids. Diuretics and, to a lesser extent, beta-blockers are the two main groups that have deleterious effects on blood triglyceride and cholesterol levels [10]. Summary of cardiovascular drug effects on circulating lipoproteins is outlined in Table 1.

Diuretics

Among cardiovascular drugs, thiazide diuretics have the most potent effect on serum lipid levels in a dose-dependent manner. Using thiazide diuretics such as hydrochlothiazide, chlorthalidone or tienilic acid in hypertensive patients is associated with elevating total cholesterol, LDL cholesterol (LDL-C), VLDL cholesterol and triglyceride levels with no significant effect on HDL cholesterol (HDL-C) [11–18]. These changes tend to occur during the first 6–12 months after starting treatment and then reach a steady state [19]. Thiazide diuretic-induced

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KEY POINTS

- Many nonlipid modifying drugs affect circulating lipids and lipoprotein metabolism.
- There is conflicting evidence from different studies in relation to the effect of many drugs.
- Diuretics, beta-blockers, antidepressants, antipsychotics, retinoic acid derivatives, testosterone and cyclosporine generally have adverse effects.
- Metronidazole, ciprofloxacin, growth hormone, alpha 1-blockers, oestrogens and progestins tend to have favourable effects.
- Discordant effects have been reported for hypoglycaemic agents.
- Although the long-term impact of these effects on lipoprotein metabolism and lipid profile on cardiovascular disease risk and progression is not known, clinicians should consider favourable and adverse effects of medications when they treat their patients, particularly those at high cardiovascular risk.

changes are likely related to reduction in insulin sensitivity and subsequent increase in lipolysis [20]. In contrast to other diuretics, indapamide (a thiazide-like diuretic) has no harmful effects on lipid profile [16,21]. Loop diuretics, especially furosemide, acutely and significantly increase atherogenic apolipoprotein B100 (apoB) containing lipoproteins and serum triglyceride levels [22]. Campbell *et al.* [22] suggested that these changes may be because of the reduction in intravascular blood volume and haemoconcentration rather than genuine changes. Torasemide, another loop diuretic, with similar effect on intravascular volume, however, lowers LDL-C concentration with no effect on total serum cholesterol and triglyceride [23].

Potassium-sparing diuretics only transiently elevate triglyceride and lower HDL-C concentrations with no other effects on lipid profile [24,25].

Beta blockers

Several authors reported undesirable effects of beta blockers on plasma lipids [10,26–32] (Table 1). Hypertriglyceridaemia is the most common dyslipidaemia occurring in patients taking beta blockers [32–34]. This is more prevalent with nonselective beta-blockers than selective beta-blockers [35]. Acebutolol and pindolol are exceptions with no obvious deleterious effect on lipid profile [36,37]. Beta-blockers potentially reduce insulin sensitivity that results in concomitant hyperinsulinaemia, which is directly related to triglyceride and inversely with HDL-C concentrations [38].

Alpha 1-blockers

Alpha 1-blockers are vasodilator antihypertensive drugs. In addition to their use in hypertension, they are also used for symptomatic treatment of benign prostatic hyperplasia. Several studies revealed favourable effects of alpha 1-blockers on lipid profile [10,39–41]. Richard *et al.* investigated the effects of different antihypertensive drugs in a randomized, double-blind, multicentre clinical trial of 902 patients followed for 4 years. Doxazosin therapy was associated with a reduction in total cholesterol, LDL-C, triglycerides and an increase in HDL-C level [5]. Concomitant uses of terazosin could ameliorate the adverse effects of diuretics on blood lipids [42].

Antiarrhythmic drugs

In a prospective study of 1567 postmyocardial infarction patients followed for 30 months, William and colleagues revealed that patients on class Ia antiarrhythmic drugs such as quinidine, procainamide and disopyramide had significantly lower cholesterol, triglyceride, apolipoprotein AII and apoB blood levels than patients on other classes of antiarrhythmic drug [43]. These class Ia antiarrhythmic drug-associated changes may be related to an alteration in ionic membrane currents at the hepatocyte level [43]. In a small study, amiodarone (a class III antiarrhythmic agent) therapy was associated with a significant decrease in triglyceride concentration in all patients, but total cholesterol decreased significantly in female patients only [44].

Other cardiovascular medications

In addition to its antiplatelet and anti-inflammatory effects, aspirin has a favourable effect on total cholesterol, triglyceride and lipoprotein (a) [Lp(a)] [45–47]. Some of these positive effects are likely related to enhancing peripheral insulin sensitivity [46]. Fenofibrate lowers triglyceride and increases HDL-C, Paradoxical reductions in HDL-C have, however, been described [48,49▪,50▪▪].

NEUROLOGICAL AND PSYCHIATRIC MEDICATIONS

Weight gain, dyslipidaemia and insulin resistance associated with antipsychotic and antidepressant therapies are major clinical challenges. Many of these medications are known to have a significant impact on eating habits [51]. Table 2 shows a summary of neurological and psychiatric medication effects.

Table 1. Cardiovascular drugs unintended effects on lipoproteins

Drug	Patient group studied	TC	LDL- C	HDL-C	Triglyceride	References
Thiazide diuretics						
Bendrofluazide	HTN	-	↔	↔	↑	Hobbs FR *et al.* 2005
Chlorthalidone	HTN	↑	↑	↔	↑	Rosenthal T *et al.* 1980, Goldman AI *et al.* 1980
Hydrochlorothiazide + Chlorthalidone	HTN, DM	↑	↔	↔	↑	Grimm RH *et al.* 1981
Hydrochlorothiazide	DM	↑	↑	↔	↔	bloomgarden TZ *et al.* 1984, Bloomgarden ZT *et al.* 1984
Indapamide	HV	↔	↔	↔	↔	Weidmann P. *et al.* 1981
Tienilic acid	HV	↔	↑	↔	↑	Weidmann P. *et al.* 1981
Loop diuretics						
Furosemide	HV	↑	↑	↑	↑	Campbell NR *et al.* 1993
Torasemide	HV	↔	↓	↔	↔	Dodion L *et al.* 1986
Potassium sparing diuretics						
Spironolactone	HTN	↔	↔	↓	↓	Falch DK and Schreiner A 1983
Beta blockers						
Acebutolol,pindolol	HTN	↔	↔	↔	↔	Lehtonen A. 1984
Atenolol	HTN	↔	↔	↓	↑	Eliasson K *et al.* 1981, Day JL *et al.* 1979
Oxprenolol	HTN	↔	↔	↔	↔	Simons LA *et al.* 1982
Propranolol	HTN	↔	-	-	↑	Day JL *et al.* 1979
Sotalol	HTN	↑	↑	↓	↑	Lehtonen A and Viikari J 1979
Alpha 1-blockers						
Doxazosin	HTN	↓	↓	↑,↔	↓	Grimm RH *et al.* 1996, Levy D *et al.* 1996
Antiarrhythmic drugs						
Amiodarone	Hypothyroidism	↑, ↔	↑	↔	↓	Kasim SE *et al.* 1990, Sonnenblick M *et al.* 1986
Disopyramide	Postinfarction	↔	↓	↔	↔	Boden *et al.* 1992
Procainamide	Postinfarction	↔	↔	↔	↓	Boden WE *et al.* 1992
Quinidine	Postinfarction	↓	↓	↔	↔	Boden WE *et al.* 1992
Antiplatelet						
Aspirin	IS, T2DM, CAD or CI	↓, ↔	↓, ↔	↓, ↔	↓, ↔	Ranga GS *et al.* 2007, Hundal RS *et al.* 2002, Akaike M *et al.* 2002

-, no data; ↓, significant decreases; ↔, no significant changes; CAD, coronary artery disease; CI, cerebral infarction; DM, diabetes mellitus; HTN, hypertension; HV, healthy volunteers. ↑, significant increases; IS, ischemic stroke; TC, total cholesterol.

Antipsychotics

These drugs are known to cause weight gain and hyperlipidaemia [52]. The degree of dyslipidaemia varies between different drugs [52]. Clonazipine and olanzapine use is associated with most marked weight gain and dyslipidaemia [52]. Risperidone and fluphenazine therapy is associated with a noticeable decrease in total cholesterol [52].

Antidepressants

Patients with depression have lower total cholesterol concentration but an atherogenic lipid profile with higher small-dense LDL particles (expressed as triglyceride per apoB ratio) compared with healthy volunteers [53]. Interestingly, this atherogenic profile improved after treatment with mirtazapine or venlafaxine [53]. Antidepressant drug effects on insulin resistance, weight and lipid profile vary significantly. Antidepressants are subdivided into the following groups.

Tricyclic antidepressants

Tricyclic antidepressant therapy is associated with weight gain and dyslipidaemia [54–57]. In an in-vitro study on cultured human hepatic cells, Raeder *et al.* [58] reported that these drugs activate sterol regulatory element-binding protein transcription

Table 2. Unintended effects of neurology and psychiatry medications on lipoproteins

Drug	Patient group studied	TC	LDL-C	HDL-C	Triglyceride	References
Antipsychotics						
Clozapine	Psychosis	↔	↔	↔	↑	Wirshing DA *et al.* 2002
Fluphenazine	Psychosis	↓	↔	↔	↔	Wirshing DA *et al.* 2002
Haloperidol	Psychosis	↔	↔	↔	↔	Wirshing DA *et al.* 2002
Olanzapine	Psychosis	↔	↓	↓	↑	Wirshing DA *et al.* 2002
Quetiapine	Psychosis	↔	↓	↔	↔	Wirshing DA *et al.* 2002
Risperidone	Psychosis	↓	↓	↔	↔	Wirshing DA *et al.* 2002
Antidepressant-TCAs						
Amitriptyline	MDD	-	-	-	↑	Kopf D *et al.* 2004
Doxepin	SRD	↑	-	-	-	Roessner V *et al.* 2004
Imipramine	PD	↔,↑	↔	↓	-	Yeragani VK *et al.* 1989
Mirtazapine	MDD,HV	↑,↔	↔	↔	↑,↔	Hummel J *et al.* 2011, Laimer M *et al.* 2006, Nicholas LM *et al.* 2003
Antidepressant-SSRI						
Citalopram	PD, MDD	↑,↔	↑	↑	↔	Bailey DL *et al.* 2003, Bilici M *et al.* 2001
Fluoxetine	MDD +/or T2DM, O/O,	↔,↓	↔	↔,↑	↔,↓	Gulseren L *et al.* 2005, Bilici M *et al.* 2001, Pedrinola F *et al.* 1996, Visser M *et al.* 1994
Fluvoxamine	MDD, Obese	↔,↓	-	-	↔	Bilici M *et al.* 2001, de Zwaan M *et al.* 1996
Paroxetine	PD, MDD+T2DM, MDD	↑,↔	↑,↔	↑,↔	↔	Gulseren L *et al.* 2005, Bailey DL *et al.* 2003, Kopf D *et al.* 2004
Sertraline	MDD,PD	↔,↑	↑	↑	↔	Bilici M *et al.* 2001, Bailey DL *et al.* 2003
Antidepressant-SNRI						
Duloxetine	DPNP	↔,↑	↔,↓	↑,↓	↔,↓	Smith T and Nicholson RA 2007, Raskin J *et al.* 2006
Naltrexone+Bupropion	O/O +T2DM	-	↔	↑	↓	Hollander P *et al.* 2013
Venlafaxine	PD, MDD	↑,↔	↑,↔	↔	↓	Hummel J *et al.* 2011
Anticonvulsant						
Carbamazepine	epilepsy	↑	↑	↓,↑	↔	El-Farahaty RM *et al.* 2015, Nikolaos T *et al.* 2004
Lamotrigine	epilepsy	↔	↑	↓	↔	El-Farahaty RM *et al.* 2015
Levetiracetam	epilepsy	↔	↑,↔	↓,↔	↔	El-Farahaty RM *et al.* 2015, Manimekalai K 2014
Oxcarbazepine	epilepsy	↑	↔	↑	↑	Manimekalai K 2014
Phenobarbital	epilepsy	↔	↔	↔	↔	Nikolaos T *et al* 2004
Phenytoin	epilepsy	↑,↔	↑	↑,↔	↑,↔	Manimekalai K 2014, Nikolaos T*et al* 2004
Topiramate	epilepsy	↔	↑	↓	↔	El-Farahaty RM *et al.* 2015
Valproic acid	epilepsy	↑,↔,↓	↑,↔,↓	↓,↔	↔,↓	El-Farahaty RM *et al.* 2015, Manimekalai K 2014, Nikolaos T *et al.* 2004

↑, significant increases; ↓, significant decreases; ↔, no significant changes; -, no data; DPNP, diabetic peripheral neuropathic pain; MDD, major depressive disorder; O/O, overweight/obese; PD, panic disorder; SRD, severe recurrent depression; T2DM, type2 diabetes mellitus; TC, total cholesterol.

factor expression in cultured liver cells leading to increased cholesterol and fatty acid biosynthesis. Medications such as clozapine, imipramine and amitriptyline, known to be associated with weight gain, induced a pronounced activation of sterol regulatory element-binding proteins compared with almost no effect for weight neutral drugs such as ziprasidone and buproprion [58].

Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors generally tend to have unfavourable effects on circulating lipoproteins (Table 2) [59–62]. Paroxetine and venlafaxine are known to elevate LDL-C level with no significant change in body weight and eating habits [59,60]. Fluoxetine has no clinically significant effects on plasma lipids in depressed patients [62].

In another study in overweight patients, fluoxetine was associated with a significant improvement in lipid profile and also a significant weight reduction in those with baseline hypercholesterolemia compared to those with normal cholesterol levels [63,64]. Furthermore, in patients with type-2 diabetes, fluoxetine lowered triglyceride levels only [65]. Mirtazapine is a sedative and also stimulates appetite associated with persistent weight gain, increasing total cholesterol with a transient hypertriglyceridaemia [66,67].

Serotonin-norepinephrine reuptake inhibitors

This class is generally regarded as the most lipid neutral among antidepressant medications [68,69] with a degree of heterogeneity [53]. Raskin *et al.* [70], however, reported a detrimental effect on lipid profile in patients with diabetic peripheral neuropathic pain.

Anticonvulsants

Carbamazepine and valproic acid are the most commonly used antiepileptic drugs. Some anticonvulsant drugs, such as carbamazepine, phenytoin, phenobarbital and primidone, are known to induce cytochrome P450 (CYP450), a hepatic enzyme with many biological roles including cholesterol biosynthesis; this may explain the dyslipidaemia associated with anticonvulsant therapy [71]. Generally, anticonvulsant drug use is associated with higher LDL-C level, no significant effect on triglyceride and variable effects on HDL-C concentration (Table 2) [72▪,73,74]. Additionally, El-Farahaty *et al.* [72▪] reported a significant increase in lipoprotein (a) up to five-fold in patients treated with anticonvulsant drugs compared with placebo.

ENDOCRINE MEDICATIONS

These drugs are analogues to endogenous hormones that either mimic the effects of hormones or exert opposite effects or small molecules (Table 3).

Anti-obesity drugs

Orlistat has beneficial effects on serum total and LDL-C levels [75,76], which are greater than might be explained by weight loss alone [77]. A small, but significant, decrease in HDL-C levels has also been reported [76], but no significant alterations in triglyceride levels [76,78].

Hypoglycaemic agents

Metformin is the recommended first-line agent in the management of type-2 diabetes [79], and is reported to reduce LDL-C [80–83], free fatty acid and triglyceride levels [80,82]. A modest increase in serum HDL-C concentrations has also been reported [82,83] although beneficial effects on lipid levels were not observed in all studies [84,85]. Discordant effects have been reported for sulphonylureas, with some studies indicating beneficial effects on total cholesterol and HDL-C [86,87] but others observing a reduction in triglyceride levels alone [80] or no favourable results [88]. Thiazolidinediones have been reported to increase LDL-C and HDL-C, while decreasing triglyceride [80,89–92]. Although these are class effects, pioglitazone actually lowers atherogenic sd-LDL [89,93–95], and has, in some studies, also been shown to reduce total cholesterol [86]. Dipeptidyl peptidase 4 inhibitors appear to have neutral effects on the lipid profile [86,96,97] although there is some evidence that Vildagliptin improves postprandial lipaemia [98] and Sitagliptin might increase HDL-C [99–102]. Glucagon-like peptide-1 agonists have been reported to have positive lipid effects although it is still unclear whether these effects are weight loss dependent [97]. Exenatide does not appear to alter the lipid profile significantly [96], but positive effects on LDL-C, HDL-C and triglyceride have been noted [103–106]. Liraglutide has also been reported to show significant triglyceride reductions [107]. Sodium glucose cotransporter-2 inhibitors appear to cause dose-related increases in total cholesterol, LDL-C and HDL-C [102,108–110]. The effect on triglyceride is more variable, with one study reporting no significant change [102], but others reductions with higher doses [108,109] or increases with lower doses [110]. The impact of these lipid changes on cardiovascular disease is currently being assessed [111]. Insulin therapy increases HDL-C and reduces circulating triglyceride levels, particularly in patients with poor glycaemic control [112]. Acute increases in insulin have also been demonstrated to promote LDL clearance from the plasma [113].

Glucocorticoids

The effect of glucocorticoids on cardiovascular disease is thought to be mediated, in part, by elevating lipoprotein levels, but contrasting effects on lipid profiles have been observed [114–116], ranging from dose-dependent adverse effects in patients with systemic lupus erythematosus [117–119] to a more favourable lipid profile with slightly higher HDL-C levels in older individuals [120]. Several small prospective studies have reported elevations of total and HDL-C levels, a neutral effect on LDL-C, and a variable response of triglyceride levels with oral corticosteroids, but no significant changes with inhaled preparations [121–124].

Table 3. Unintended effects of endocrine medications on lipoproteins

Drug	Patient group studied	TC	LDL-C	HDL-C	Triglyceride	References
Anti-obesity medications						
Orlistat	Primary hyperlipidaemia, obesity	↓	↓	↓,↔	↔	Tonstad S *et al.* 1994, Davidson MH *et al.* 1999, Rucker D *et al.* 2007
Oral hypoglycaemic agents – biguanides						
Metformin	T2DM, PCOS	↓,↔	↓	↑, ↔	↓,↔	Bailey CJ *et al.* 1996, Wulffele MG *et al.* 2004, Bolen S *et al.* 2007, Lord JM *et al.* 2003
Oral hypoglycaemic agents – sulphonylureas						
Glibenclamide	T2DM	↔,↓	↔,↓	↔	↔,↓	Buse JB *et al.* 2004
Gliclazide	T2DM	↓	↔	↔	↓	Buse JB *et al.* 2004
Glimepiride	T2DM	↔	↔	↔	↔	Buse JB *et al.* 2004
Oral hypoglycaemic agents – thiazolidinediones						
Piogltazone	T2DM	↓,↑	↑	↑	↓	Goldberg RB *et al.* 2005, Dormandy JA *et al.* 2005, Betteridge DJ *et al.* 2007, Bergenstal RM *et al.* 2010
Oral hypoglycaemic agents – DPP-4 inhibitors						
Saxagliptin	T2DM	↔	↔	↔	↔	Boland CL *et al.* 2013
Sitagliptin	T2DM	↓,↔,↑	↓,↔,↑	↔,↑	↓,↑	Charbonnel B *et al.* 2006, Scott R *et al.* 2008, Wainstein J *et al.* 2012, Monami M *et al.* 2012, Boland CL *et al.* 2013, Lavalle Gonzalez FJ *et al.* 2013
Vildagliptin	T2DM	↓,↔	↓,↔	↓,↔	↓	Matikainen N *et al.* 2006
Oral hypoglycaemic agents – SGLT2 inhibitors						
Canagliflozin	T2DM	↑	↑	↑	↑	Lavalle-Gonzalez FJ *et al.* 2013, Forst T *et al.* 2014
Dapagliflozin	T2DM	↑,↔	↑, ↔	↑,↔	↓,↔	Bailey CJ *et al.* 2010, Ferrannini E *et al.* 2010
Injectable hypoglycaemic agents – GLP-1 agonists						
Exenatide	T2DM	↓,↔	↓,↔	↑,↔	↓	Blonde L *et al.* 2006, Ratner RE *et al.* 2006, Schwartz EA *et al.* 2010, Bergenstal RM *et al.* 2010
Liraglutide	T2DM	↔	↔	↔	↓	Vilsboll T *et al.* 2007
Injectable hypoglycaemic agents						
Insulin	T2DM	↔	↔,↓	↑, ↔	↓	Mihailescu DV *et al.* 2011
Corticosteroids						
Prednisolone	RA, SLE	↑	↔,↑	↔,↑, ↓	↔, ↑	Ettinger WH *et al.* 1987, Boers M *et al.* 2003, Choi HK *et al.* 2005, Petri M *et al.* 1992, MacGregor AJ *et al.* 1992, Leong KH *et al.* 1994
Endocrine medications						
Eprotirome	Dyslipidaemia	↓	↓	↔	↔,↓	Berkenstam A *et al.* 2008, Ladenson PW *et al.* 2010
Levothyroxine	Hypothyroidism, subclinical hypothyroidism	↓, ↔	↓, ↔	↓, ↔	↓, ↔	Muls E *et al.* 1984, O'Brien T *et al.* 1993, Danese MD *et al.* 2000, Villar HC *et al.* 2007
Growth hormone	Growth hormone deficiency, hypopituitarism	↓, ↔	↓, ↔	↓,↔,↑	↔,↓	Russell-Jones DL *et al.* 1994, Johannsson G *et al.* 1995, Al-Shoumer KA *et al.* 1998, Gotherstrom G *et al.* 2001, Beshyah SA *et al.* 1995, Miller KK *et al.* 2010
Testosterone	Hypogonadism, healthy older men	↔,↓	↔,↓	↔,↓	↔	Thompson PD *et al.* 1989, Zitzmann M 2007, Basaria S *et al.* 2010
Androgen-deprivation therapy	Prostate cancer	↔,↑	↔	↔,↑	↔,↑	Smith JC *et al.* 2001, Dockery F *et al.* 2003, Saylor PJ *et al.* 2013, Harrington JM *et al.* 2014

Table 3 (*Continued*)

Drug	Patient group studied	TC	LDL-C	HDL-C	Triglyceride	References
Combined oral contraceptives	Contraception	↓	↓	↓,↑	↓,↑	LaRosa JC 1989, Burkman RT *et al.* 1988, Godsland IF *et al.* 1990, Mantel-Teeuwisse 2001
Norethisterone	Contraception	↔	↔	↔,↓	↔	Godsland IF *et al.* 1990, Fahmy K etal 1991, Garza-Flores J *et al.* 1991, Enk L *et al.* 1992
Oestradiol	Postmenopausal women	↓	↓	↑	↑	Rijpkema AH *et al.* 1990, Walsh BW *et al.* 1991
Raloxifene	Postmenopausal women	↓	↓	↔	↔	Draper 1996, Delmas 1997, Walsh BW *et al.* 1998
Tamoxifen	Breast cancer	↓	↓	↔	↔,↑	Grey AB *et al.* 1995, Hozumi Y *et al.* 1998, Benshushan A and Brzezinski A, 1999

-, no data; ↑, significant increases; ↓, significant decreases; ↔, no significant changes; GLP1, glucagon-like peptide-1; O/O, overweight/obese; PCOS, polycystic ovary syndrome; RA, rheumatoid arthritis; SGLT2, sodium-glucose cotransporter 2; SLE, systemic lupus erythematosus; T2DM, type 2 diabetes mellitus; TC, total cholesterol.

Thyroid hormones

Treatment with levothyroxine in patients with hypothyroidism reduces LDL-C, triglyceride and lipoprotein (a) levels but also modestly decreases HDL-C [125–127]. A meta-analysis of 13 studies of subclinical hypothyroidism found that thyroxine therapy resulted in significant reductions of serum total cholesterol and LDL-C but no significant effects on serum HDL-C or triglyceride [128]. More recently, a Cochrane review found no significant effect on total cholesterol, LDL-C, HDL-C or triglyceride by thyroid hormone replacement with levothyroxine in subclinical hypothyroidism [129]. The thyromimetic Eprotirome appears to be able to reduce serum lipid levels with dose-dependent reductions in LDL-C, apoB, Lp(a) and triglyceride [130]. An earlier study reported reductions in total and LDL-C but no significant changes in HDL-C, triglyceride or Lp(a) [131]. Eprotrome development was terminated because the animal toxicology study demonstrated damage to cartilage in dogs that were given eprotirome for up to 12 months.

Growth hormone

Studies on the effects of treatment with recombinant human growth hormone on serum lipids have given conflicting results, with some studies reporting decreased levels of total cholesterol and LDL-C [132–140] while others reported no change [141–144]. Triglyceride levels remain unchanged. Studies show inconsistent results regarding the effects on HDL-C [132–134,139,140,145,146]. In two studies Lp(a) concentrations increased with growth hormone therapy [146,147] although a third found no effect [145].

Testosterone

Observational and Mendelian randomization studies have produced conflicting results on the association between lower endogenous testosterone levels and lipoprotein effects [148–155,156▪]. The effect of testosterone replacement therapy on lipid profile appears similarly complex [112], with reports of reductions in LDL-C but variable changes in HDL-C and triglyceride [157–160]. In a meta-analysis of randomized controlled trials, testosterone treatment was associated with a significant small reduction in HDL-C with no effect on LDL-C among men [152] but increased LDL-C among women [161]. Testosterone therapy in transgender persons significantly increases LDL-C and triglyceride and significantly decreases HDL-C [162]. Short-term prospective studies of androgen deprivation therapy have failed to demonstrate consistent effects on lipids, noting increased or unchanged LDL-C, HDL-C and triglyceride levels [152,156▪,163–167]. Treatment with Gonadotropin-Releasing Hormone (GnRH) antagonists and agonists without the addition of antiandrogens has, however, been reported to result in significant adverse changes in total cholesterol, triglyceride and HDL-C [168].

Oestrogens and progestins

Unopposed oestrogens beneficially affect the lipid profile, lowering total cholesterol and LDL-C and elevating HDL-C levels [169–174]. Unopposed oestrogens can, however, also significantly elevate triglyceride levels in a dose-dependent manner [171,175]. The synthetic oestrogen ethinyloestradiol has a stronger beneficial effect than natural oestrogens [169]. Oestrogen implants show the same but weaker pattern on total cholesterol,

LDL-C and HDL-C, although a reversal of the beneficial effect on HDL-C has been reported [174,176]. Transdermal oestrogens have almost no effects on serum lipid levels [171,174,176,177]. Oestrogen therapy in transgender persons reduces LDL-C, HDL-C and triglyceride levels [162]. The low doses of Norethisterone used in progestogen-only contraceptive pills showed no significant effects on the lipid profile [178,179] and depot formulations only lowered HDL-C [180,181]. Depot medroxyprogesterone also lowers HDL-C [180,182,183].

Combined oestrogen/progestogen hormone replacement therapy has similar effects on total cholesterol and LDL-C levels as unopposed oestrogens [169–171,173,174]. The effects on HDL-C levels are blunted (combinations with medroxyprogesterone or dydrogesterone) or even reversed (combinations with norethisterone). Variable effects on triglyceride levels have been reported [169,170,173,174]. Significant reductions in Lp(a) levels have also been described [184,185]. The effects of combined oral contraceptives on serum lipid levels depend on the oestrogen dose and the androgenicity of the progestogen [186,187]. Formulations with levonorgestrel increase LDL-C and triglyceride significantly, and decrease HDL-C levels [178,188]. Preparations with other 'second generation' progestogens show similar effects on total cholesterol, LDL-C and triglyceride levels, but effects on HDL-C may be more beneficial [178,189]. Formulations with 'third generation' progestogens (desogestrel and gestodene) show favourable effects on LDL-C and HDL-C, but also significantly increase triglyceride levels [178,186,190,191]. Transdermal preparations are not associated with the same increase in triglyceride levels [192].

Oestrogen receptor antagonists

Tamoxifen decreases both total cholesterol and LDL-C levels, with no change in HDL-C [193,194]. Reported changes in triglyceride levels vary from no effect to a significant increase [193,195]. In postmenopausal women the selective oestrogen receptor modulator Raloxifene decreases total cholesterol and LDL-C levels [196–199] while HDL-C and triglyceride levels remain unchanged [187].

MISCELLANEOUS

Many other medications have been reported to affect circulating lipoproteins.

Antiretroviral drugs

Protease inhibitors are associated with unfavourable changes in the lipid profile, primarily a rise in total cholesterol and triglycerides [200]. The combination of metabolic abnormalities, including lipodystrophy, hyperlipidaemia and insulin resistance known as 'lipodystrophy syndrome', is a common complication of HIV infected patients treated with protease inhibitors [201]. Indeed, several long-term studies revealed that protease inhibitor therapy is associated with a potent hyperglycaemia and dyslipidaemia effects [202,203]. Ritonavir was found to be more strongly associated with hypertriglyceridaemia than the others [204–206].

Antibiotics

The effect of antibiotics on lipoproteins was initially highlighted in the 1970s and 1980s. In one of the earliest studies, Samuel *et al.* [207] found a reduction in total cholesterol in a small number of patients with neomycin, kanamycin, chloramphenicol and chlortetracycline taken for 2 weeks. This reduction in cholesterol was accompanied by inhibition of 7a-dehydroxylation of cholic acid, suggesting that a reduction in colonic bacterial activity leading to alteration in bowel flora. This was proposed as the mechanism for reduction in cholesterol.

In a small study of five patients with Crohn's disease serum total cholesterol level decreased significantly after 1 year of metronidazole treatment [208] and two other studies reported a significant reduction in LDL-C [209,210]. Metronidazole reduced biliary secretion of cholesterol and bile acids by 13 and 20%, respectively, suggesting a decrease in sterol synthesis in addition to a significant reduction in intestinal cholesterol absorption by 22% [209,210]. In a short-term study, high dose metronidazole showed no effect [211]. More recently, Jenkins *et al.* [212], however, studied the effects of metronidazole and ciprofloxacin on lipids over 10 days in 22 subjects. They found that metronidazole significantly reduced LDL-C, oxidized LDL, LDL-C to HDL-C and apolipoprotein B to apolipoprotein A-I ratio [212]. The reduction in LDL-C was related to an increase in bifidobacteria but not to markers of colonic fermentation. Ciprofloxacin only significantly reduced apoB without affecting other lipid markers [212]. All these were small studies of short duration.

Vitamins

Isotretinoin, also known as 13-cis retinoic acid, is a synthetic vitamin A. It has several potential side-effects such as liver enzyme alteration and dyslipidaemia. Several studies demonstrated that isotretinoin increases triglyceride, total cholesterol and LDL-C and decreases HDL-C levels [213–215].

Bexarotene is another synthetic retinoid used to treat advanced stages of cutaneous T-cell lymphoma, and is associated with hyperinsulinaemia, hypothyroidism and dyslipidaemia. It raises total cholesterol, LDL-C and triglyceride and lowers HDL-C. Bexarotene-induced dyslipidaemia can be severe with triglyceride levels more than 11 mmol/l [216,217].

There is controversy about the effect of vitamin D on lipid profile and cardiovascular disease. Serum 25(OH) vitamin D level is positively associated with HDL-C, and negatively with triglyceride in cross-sectional studies. Vitamin D supplementation in overweight subjects and postmenopausal women, however, increased LDL-C and reduced triglycerides levels [218–220].

In a weight loss program over 15 weeks, investigators showed that administration of calcium and vitamin D led to a significant reduction in total cholesterol, LDL-C and LDL-C:HDL-C in the group taking calcium and vitamin D compared with those who did not [221]. These changes were independent of changes in fat mass and waist circumference [221]. Zemel *et al.* [222] demonstrated that dietary calcium inhibits lipogenesis and stimulates lipolysis in adipose tissues leading to a reduction in body fat.

Moreover, there is an inverse relationship between dietary calcium intake and total cholesterol and LDL-C levels [223]. In a pilot, double-blind, placebo-controlled trial conducted by Chai *et al.* [224], there was a significant reduction in serum triglycerides in those on calcium and on calcium plus vitamin D3 when compared with placebo. Jorde and Grimnes [218] recently found inconclusive evidence about the effects of vitamin D and calcium supplementation on lipid profile. Several studies reported no significant effect of vitamin D replacement on lipid profile. Nevertheless, it is important to mention change in lipid profile was a secondary outcome in these studies [225–232].

Cyclosporin

This is an immunosuppressant drug commonly used in patients undergoing organ transplantation. Hyperlipidaemia is a common side-effect of cyclosporine [233].

CONCLUSION

Dyslipidaemia is one of the common side-effects of many drugs with varied severity dependent on the dose and duration of the therapy. These deleterious changes should be taken into consideration, especially in patients at high risk of cardiovascular disease, with close monitoring. Other drugs have a positive effect on circulating lipoproteins, but, generally, it is not clear if this will lead to reductions in cardiovascular disease outcome or progression.

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Conflicts of interest

There are no conflicts of interest.

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Olmesartan medoxomil (CS-866)

An angiotensin II receptor blocker for treatment of hypertension

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ABSTRACT

Olmesartan medoxomil (CS-866) is an angiotensin II receptor blocker under FDA review for treatment of hypertension. It is a tetrazolylbiphenyl-substituted imidazole derivative that undergoes de-esterification to form its active metabolite, olmesartan. The steady-state AUC and peak plasma concentration of olmesartan increase linearly with dose. The drug's absolute bioavailability is 26%, which falls in the middle of the range seen with the six FDA-approved ARBs (losartan, valsartan, irbesartan, candesartan, eprosartan, and telmisartan). Like the six other ARBs, olmesartan medoxomil can be taken once daily without regard to meals. Placebo-controlled trials have established its safety and efficacy at doses from 2.5 to 80 mg once daily in patients with mild to moderate hypertension. In addition, a comparative trial has shown olmesartan medoxomil to have a more potent antihypertensive effect than losartan and valsartan. Its dose-response curve plateaus at 20 to 40 mg. Because this agent does not undergo P-450–mediated biotransformation, its likelihood of drug interactions is minimal.

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Each month, our Focus column reviews a recently approved or investigational drug of Formulary Committee interest. The column is coordinated by Robert A. Quercia, MS, director of drug information services, Hartford (CT) Hospital, and associate clinical professor, University of Connecticut School of Pharmacy, Storrs; and by Moses S.S. Chow, PharmD, professor and director, school of pharmacy, faculty of medicine, Chinese University of Hong Kong, and director of collaborative research, department of pharmacy, Hartford Hospital.

Approximately 50 million Americans have hypertension, and only 29% achieve blood pressure control within the target level of less than 140/90 mm Hg.[1,2] Hypertension indirectly imposes an enormous burden on society, with annual expenditures exceeding $259 billion in the United States for heart failure and stroke, two common outcomes associated with hypertension.[2]

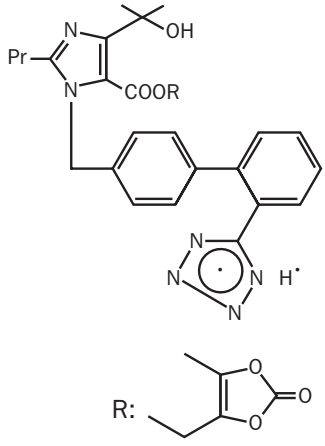
Angiotensin-converting enzyme (ACE) inhibitors have been available for blockade of the renin-angiotensin-aldosterone system (RAAS) for nearly two decades.[3] The ACE inhibitors are widely used in the management of essential hypertension, myocardial infarction, diabetic nephropathy, and chronic heart failure.[4] However, approximately 5% to 10% of patients who receive ACE inhibitors develop a dry cough following therapy.[4] Furthermore, angiotensin II can be generated by non–ACE-dependent pathways catalyzed by other enzymes, including cathepsin G, elastase, tissue plasminogen activator, chymostatin-sensitive angiotensin II generator enzyme, and chymase.[4]

Angiotensin II receptor blockade offers an alternative approach to RAAS blockade. Through antagonism of the angiotensin II type 1 receptor (AT_1), angiotensin II receptor blockers (ARBs) induce absolute inhibition of angiotensin II activity.[5] In addition, since ARBs do not inhibit degradation of bradykinin and substance P, cough is less likely to result.[5] To date, six ARBs have been approved by the FDA to treat hypertension: losartan, valsartan, irbesartan, candesartan, eprosartan, and telmisartan.[5] Recently, a new investigational ARB, olmesartan medoxomil (also known as CS-866), has been developed by Sankyo Pharma and studied for use in hypertension. A New Drug Application for olmesartan medoxomil was submitted to the FDA in July 2000, and approval for US marketing was pending at press time. This article reviews the pharmacologic, pharmacokinetic, and therapeutic aspects of this new agent in the context of the currently available ARBs.

Chemistry and Pharmacology

All of the FDA-approved ARBs, with the exception of valsartan, are imidazole derivatives.[6-11] Olmesartan medoxomil is characterized by a tetrazolylbiphenyl group at the 1-position, a propyl group at the 2-position, a hydroxyalkyl substituent at the 4-position, and an ester group at the 5-position.[12] Structure-activity studies of imidazole derivatives have shown that the lipophilic biphenyl substituent at the 1-position and a linear alkyl group at the 2-position display strong binding affinities with hydrophobic pockets of the angiotensin II receptor. Moreover, the addition of a tetrazole substituent to the 1-position of the biphenyl group further enhances antagonist activity.[12] Other ARBs with tetrazolylbiphenyl-substituted imidazole groups are losartan, candesartan, and irbesartan.[6,7,10] Valsartan has a biphenyl group, telmisartan is a biphenyl-substituted benzimidazole, and eprosartan is a nonbiphenyl-, nontetrazole-substituted imidazole.[8,9,11] It is unclear whether structural differences among the ARBs translate into clinically significant effects, but more research is needed.

Recent research has been directed toward characterizing ARBs' binding to the AT_1 receptor. Of special interest is the classification of the AT_1-bind-



Chemical structures of olmesartan and olmesartan medoxomil

Formulary/Source: Reference 16

ing capacity of ARBs into two categories, noncompetitive and competitive.[13] Noncompetitive antagonism indicates suppression of agonist response despite escalations in agonist concentration. The reverse holds true for competitive antagonism.[13] Olmesartan medoxomil, like candesartan, valsartan, and telmisartan, has been shown to be a noncompetitive AT_1 antagonist.[7,13-16] Whether noncompetitive antagonism provides superior protection from angiotensin II has yet to be determined.

Olmesartan medoxomil is de-esterified in the gastrointestinal tract to form its active metabolite, olmesartan (also referred to as RNH-6270). Angiotensin II binding studies with bovine adrenal cortex showed that the concentration of olmesartan required to produce 50% inhibition of angiotensin II binding (IC_{50}) for the AT_1 receptor was 7.7 ± 1.0 nM.[16] In the same binding studies, the IC_{50} values of losartan and its active metabolite, EXP-3174, were 92 ± 5 nM and 16 ± 1 nM, respectively. The IC_{50} values of eprosartan, valsartan, and candesartan range from 1.9 nM to 29 nM.[7-9] However, since different animal models were used in the binding studies with eprosartan, valsartan, and candesartan, the cross-comparability of the binding affinities to the AT_1 receptor is limited. Also, although IC_{50} values provide an indication of angiotensin II inhibition, it is unclear whether there is a direct correlation between these values and antihypertensive efficacy.

Pharmacokinetics

The pharmacokinetic properties of olmesartan medoxomil have mainly been determined in healthy male volunteers.[17] In a single-dose (10 to 160 mg) oral study in 40 healthy males,[17] the time to achieve maximum plasma concentrations (T_{MAX}) of olmesartan ranged from 1.4 ± 0.5 to 2.8 ± 1.1 hours, with no evidence of dose dependence. Peak plasma concentrations (C_{MAX}) of olmesartan were dose-proportional, ranging from 224 ± 45 to 2,100 ± 532 ng/ml. Similarly, the area under the plasma concentration–time curve ($AUC_{0-\infty}$) increased with dose and ranged from 1,631 ± 266 to 19,905 ± 4,370 ng•hr/ml. The terminal elimination half-life of olmesartan ranged from 11.8 ± 2.3 to 14.7 ± 5.0 hours. After a single oral dose of olmesartan medoxomil, urinary recovery rates of olmesartan were approximately 7% to 11%.

The steady-state pharmacokinetics of olmesartan medoxomil were studied in a randomized, double-blind, placebo-controlled trial in 30 healthy males.[17] The drug was given in doses of 20, 40, or 80 mg once daily for 10 days. Both C_{MAX} and AUC_{0-24} for olmesartan increased linearly with dose escalation, ranging from 507 ± 58 to 1,379 ± 255 ng/ml and from 2,950 ± 378 to 9,382 ± 2056 ng•hr/ml, respectively. Renal clearance of olmesartan after 10 days was not affected with increasing doses and ranged from 0.64 to 0.75 l/hr.

The volume of distribution and urinary recovery rates of olmesartan were determined in a single-dose study in 34 healthy male volunteers who received 1, 2, 4, 8, 16, or 32 mg of olmesartan intravenously.[17] The volume of distribution did not exhibit dose-dependent variations and ranged from 14.7 ± 3.5 to 19.7 ± 5.3 liters. Urinary recovery rates were 35% to 49% after single intravenous olmesartan doses (1 to 32 mg).

The absolute bioavailability of olmesartan medoxomil was determined in a two-way crossover study in 24 healthy male volunteers.[17] Subjects received 16 mg of olmesartan or the equivalent amount of olmesartan medoxomil orally in random order, with a washout pe-

TABLE 1

PHARMACOKINETICS OF AVAILABLE ARBs AND OLMESARTAN (ACTIVE METABOLITE OF OLMESARTAN MEDOXOMIL)

Drug	T_{MAX} (hr)	F (%)	$t_{1/2}$ (hr)	V_d (liters)	Food-drug interactions	Elimination
Losartan[5,6]	1 (3–4)*	33	2 (4–6)*	34 (12)*	No	60% fecal; 35% urine
Valsartan[5,9]	2	23	7	17	No	83% fecal; 13% urine
Irbesartan[5,10,18]	1–2	60–80	12–20	53–93	No	80% fecal; 20% urine
Candesartan[5,7]	3–5	42	9–13	0.13 l/kg	No	67% fecal; 33% urine
Eprosartan[5,8,18]	2–6	13	5–7	308	No	90% fecal; 7% urine
Telmisartan[5,11,18]	1	43	24	500	No	>98% fecal
Olmesartan[17]	1.4–2.8	26†	11.8–14.7	14.7–19.7	No	35%–49% urinary recovery rate‡

* Values in parentheses are for EXP-3174, the active metabolite of losartan.

† For olmesartan medoxomil

‡ For intravenous olmesartan

T_{MAX} = time to maximum plasma concentration; F = absolute bioavailability; $t_{1/2}$ = terminal elimination half-life; V_d = volume of distribution

Formulary/Source: References 5–11, 17, and 18

TABLE 2

OVERVIEW OF AVAILABLE CLINICAL HYPERTENSION STUDIES OF OLMESARTAN

	Reference 20	Reference 21	Reference 22
Patient demographics	334 pts (90% nonblack, 10% black) with mean daytime DBP ≥ 90 mm Hg	18 pts (8 male, 10 female) with mild to moderate hypertension	76 hypertensive pts with DBP > 90 mm Hg on at least 30% of DBP readings
Design	■ Randomized, double-blind, placebo-controlled, parallel-group ■ 2-wk to 3-wk placebo run-in	■ Dose titration ■ Placebo run-in of ≥ 4 wk	■ Randomized, double-blind, placebo-controlled, parallel-group ■ 2-wk placebo run-in
Regimens	■ Placebo × 8 wk ■ OLM 5, 20, or 80 mg qd × 8 wk ■ OLM 2.5, 10, or 40 mg bid × 8 wk	OLM titrated from 5 to 40 mg/d and continued for 12 mos	■ Placebo × 6 wk ■ OLM 20 mg qd × 6 wk ■ OLM 80 mg qd × 6 wk
Endpoint(s)	Mean change in DBP from baseline to 8 wk (measured by ABPM)	Mean changes in sitting SBP and DBP from baseline to 3, 6, and 12 mos	Mean changes in DBP from baseline to 3 and 6 wk (measured by ABPM)
Results	■ 24-hr DBP lowered by 9.3, 11.2, and 9.9 mm Hg with OLM 5, 20, and 80 mg qd, respectively ■ 24-hr DBP lowered by 7.9, 10.7, and 10.7 mm Hg with OLM 2.5, 10, and 40 mg bid, respectively	■ DBP lowered by 13, 16, and 14 mm Hg at 3, 6, and 12 mos, respectively ($p < 0.01$ vs baseline) ■ SBP lowered by 25, 31, and 25 mm Hg at 3, 6, and 12 mos, respectively ($p < 0.01$ vs baseline)	■ OLM 20 mg: 24-hr DBP lowered by 10 and 9 mm Hg at 3 and 6 wk, respectively ($p < 0.05$ vs placebo) ■ OLM 80 mg: 24-hr DBP lowered by 8 and 9 mm Hg at 3 and 6 wk, respectively ($p < 0.05$ vs placebo)
Conclusions	No difference between once- and twice-daily dosing of OLM. Doses of 5 to 80 mg are effective, with no additional benefit beyond 20 mg.	OLM's peak blood pressure–lowering effects are achieved by 3 mos	OLM's peak blood pressure–lowering effects are seen by 3 wk. No additional lowering seen with doses exceeding 20 mg.

ABPM = ambulatory blood pressure monitoring; DBP = diastolic blood pressure; OLM = olmesartan; SBP = systolic blood pressure

Formulary/Source: Adapted from references 20–22

riod of at least 7 days between treatments. Olmesartan medoxomil was found to have an absolute bioavailability of 26%, which is comparable to that of valsartan (23%).[18] Among the ARBs, eprosartan has the lowest absolute bioavailability (13%) and irbesartan has the greatest (60% to 80%).[18]

The effect of food on the bioavailability of oral olmesartan medoxomil has been studied in healthy volunteers (data on file, Sankyo Pharma). Twenty-four male subjects received single 20-mg doses after fasting and after food ingestion. The C_{MAX} and $AUC_{0-\infty}$ increased by only 3.6% after food intake. Consequently, like the six FDA-approved ARBs,[5] olmesartan medoxomil can be taken without regard to meals. Table 1 summarizes some of the pharmacokinetic properties of olmesartan medoxomil (ie, olmesartan)* in comparison with the six available ARBs.

Clinical Trials

Placebo-controlled trials. Olmesartan's safety and efficacy have been evaluated in 2,540 and 2,145 patients, respectively, treated with the drug.[19] A recent integrated data analysis by Neutel[19] included antihypertensive efficacy findings from seven randomized, double-blind, placebo-controlled, parallel-group clinical trials (N = 2,693) of olmesartan in patients with mild to moderate hypertension (diastolic blood pressure [DBP] of 100 to 115 mm Hg). All were multicenter US or European trials. The studies evaluated olmesartan doses ranging from 2.5 to 80 mg/day given for 6 to 12 weeks. The analysis showed that all doses of olmesartan induced significantly greater reductions in DBP and systolic blood pressure (SBP) at the primary study time point than did placebo ($p < 0.001$). Mean reductions from baseline in olmesartan-treated patients ranged from 9.6 to 14.0 mm Hg for DBP and 11.3 to 18.0 mm Hg for SBP.[19] Three of these seven trials have been published to date (all in abstract form);[20-22] table 2 summarizes these studies.

The onset of olmesartan's antihypertensive effect has been shown to be rapid, with most of the blood pressure reduction achieved within 3 weeks of treatment initiation.[22] Two of the published clinical trials to date have compared 20-mg and 80-mg daily doses of olmesartan;[20,22] these trials, both of which employed ambulatory blood pressure monitoring, showed no differ-

* For brevity, "olmesartan" (technically the name of the active metabolite) will hereafter be used to refer to "olmesartan medoxomil."

TABLE 3

DOSING PARAMETERS FOR AVAILABLE ARBs AND OLMESARTAN

Drug	Initial dose (mg/d)	Maintenance dose (mg/d)	Dose-response plateau (mg)	Trough-to-peak ratio (%)
Losartan[5]	50	50–100	50	58–78
Valsartan[5]	80	80–320	80	69–76
Irbesartan[5]	150	150–300	300	>60
Candesartan[5]	8–16	8–32	32	80
Eprosartan[5]	600	400–800	400	67
Telmisartan[5]	40	20–80	40–80	≥97
Olmesartan[19,20,22]	20	20–40	20–40	57–70

Formulary/Source: References 5, 19, 20, 22, and 24

ence in blood pressure reduction between the two doses. In fact, one of the studies[20] found that the 20-mg dose was associated with a 1.3–mm Hg greater reduction in DBP than the 80-mg dose.

A clinically significant difference in antihypertensive effect is delineated by blood pressure differences exceeding 2 mm Hg.[23] Neutel's integrated efficacy analysis of olmesartan[19] showed that patients treated with 40 mg once daily experienced an additional 3.1–mm Hg reduction in sitting SBP compared with the 10-mg dose. Thus, the dose-response curve for olmesartan appears to reach its plateau at 20 to 40 mg. With the exception of candesartan and irbesartan, the other ARBs appear to exhibit flat dose-response curves (table 3).[5,19,24]

Comparative trials. In the past few years, studies comparing the antihypertensive effects of various ARBs have shown that candesartan 16 mg once daily and irbesartan 300 mg once daily induce superior blood pressure reductions compared with losartan 50 mg once daily.[5] A recent randomized, double-blind, parallel-group study[25] compared the antihypertensive effects of once-daily treatment with olmesartan 20 mg (n = 145), losartan 50 mg (n = 146), valsartan 80 mg (n = 142), and irbesartan 150 mg (n = 145) on sitting DBP. Following 8 weeks of therapy, olmesartan reduced sitting DBP by 3.3 mm Hg more than losartan (p = 0.0002) and 3.6 mm Hg more than valsartan (p = 0.0000). Olmesartan reduced sitting DBP by 1.6 mm Hg more than irbesartan (p = 0.0412), but since the difference was less than 2 mm Hg, it was not clinically significant.

Trough-to-peak ratio. In the 8-week placebo-controlled study that compared once-daily with twice-daily dosing of olmesartan,[20] DBP trough-to-peak (T:P) ratios for 5 to 80 mg once daily ranged from 57% to 70%.[19] The T:P ratio is calculated by dividing the trough blood pressure reduction from baseline by the peak blood pressure reduction within the dosing interval.[5] A T:P ratio greater than 50% validates once-daily dosing since the trough antihypertensive effect is less likely to be a residual of a large peak effect.[5] Hence, once-daily dosing is appropriate for olmesartan, as it is for all the available ARBs (see table 3 for T:P ratios).

Use of ARBs for heart failure. Currently, none of the available ARBs is approved by the FDA for treatment of chronic heart failure, although they are increasingly being studied for this use.[5] Presently, however, there are no ongoing clinical trials of olmesartan in patients with heart failure.

To date, only losartan and valsartan have been evaluated in published heart failure trials with all-cause mortality as the primary endpoint. The recent ELITE II (Evaluation of Losartan in the Elderly II) trial compared losartan with the ACE inhibitor captopril in 3,152 patients with New York Heart Association (NYHA) class II to IV heart failure.[26] While there was no significant difference between the treatments in all-cause mortality, the withdrawal rate was significantly lower in the losartan group. The authors concluded that losartan should be reserved for heart failure patients unable to tolerate ACE inhibitor therapy. More recently, valsartan was evaluated for treatment of NYHA class II and III heart failure in the 5,010-patient, placebo-controlled Valsartan Heart Failure Trial (Val-HeFT).[27] While valsartan did not improve all-cause mortality, it significantly reduced the incidence of another primary endpoint, all-cause mortality plus morbidity, by 13.3% relative to placebo (p = 0.009). Interestingly, patients who were not on ACE inhibitors at baseline experienced a 45% reduction in the combined endpoint of all-cause mortality plus morbidity with valsartan relative to placebo.

Adverse Effects

The recent integrated data analysis by Neutel[19] included a safety analysis among the 2,540 hypertensive patients who received olmesartan (2.5 to 80 mg/day) in seven placebo-controlled trials. The most frequently reported adverse effects were headache (5.6% incidence), upper respiratory tract infection (3.3%), influenza-like symptoms (3.1%), dizziness (2.8%), and bronchitis (2.0%). The only effect reported at more than a 1-percentage point greater frequency in olmesartan-treated patients than placebo recipients was dizziness (2.8% vs 0.9%, respectively).

Comparative safety considerations between ARBs and ACE inhibitors. Approximately 3% of ACE inhibitor–naive patients who take losartan experience cough, which is comparable to the incidence in placebo-treated patients.[28] A multicenter, randomized, double-blind trial by Lacourcière et al[29] evaluated losartan and the ACE inhibitor lisinopril in patients with a known history of ACE inhibitor–induced cough. Cough was reported in 72% and 29% of patients taking lisinopril and losartan, respec-

Formulary Considerations

▶ The angiotensin II receptor blocker (ARB) class has expanded considerably over the past 6 years. Selection of an ARB for antihypertensive therapy should be directed by pharmacologic, pharmacokinetic, and therapeutic differences among the various agents. Olmesartan, like the currently available ARBs, can be taken once daily without regard to meals. In addition, since it does not undergo cytochrome P-450–mediated biotransformation to its active metabolite, the likelihood of drug interactions is minimal.

Clinical trials have established olmesartan's safety and efficacy at doses from 2.5 to 80 mg once daily in patients with mild to moderate hypertension. In addition, olmesartan 20 mg appears to exert superior blood pressure reduction compared with losartan 50 mg and valsartan 80 mg. Of note, candesartan 16 mg and irbesartan 300 mg have been shown to induce greater blood pressure reductions than losartan 50 mg. Future trials should compare the antihypertensive efficacy of olmesartan 40 mg, candesartan 16 to 32 mg, and irbesartan 300 mg.

In summary, olmesartan appears to share similar advantages with candesartan and irbesartan in terms of therapeutic efficacy. While further research is needed to establish its role in other diseases, such as heart failure, its antihypertensive efficacy has already been established by numerous trials. Olmesartan's pricing relative to candesartan and irbesartan may ultimately determine whether it will be added to hospital and managed care formularies.

tively. One proposed mechanism for cough recurrence is cross-reactivity between ACE inhibitors and ARBs.[29]

Angioedema is a rare and potentially life-threatening adverse effect associated with ACE inhibitor therapy.[30] The incidence of ACE inhibitor–induced angioedema is estimated to be 0.1% to 0.2% in Caucasians and about three times higher in African Americans.[30] Various mechanisms for angioedema have been proposed, including bradykinin accumulation, histamine release from mast cells, and substance P accumulation.[30] Nineteen published cases of ARB-induced angioedema have been reported thus far (18 with losartan, 1 with valsartan); patients in 32% of these cases had prior exposure to ACE inhibitor therapy.[31] Losartan was the first ARB to be approved by the FDA (1995), which could account for its association with a larger number of cases.[5] Until more is known about the exact mechanism responsible for angioedema, caution should be exercised when ARB therapy is initiated in patients with a history of angioedema.

Drug Interactions

Drug interactions should be considered when selecting among ARBs. No drug interaction studies of olmesartan have yet been published, but several studies have been performed to test for interaction of olmesartan with digoxin, warfarin, and antacids (data on file, Sankyo Pharma). No effects on the pharmacokinetics or pharmacodynamics of either olmesartan or the test drug were noted in any of these studies. Since olmesartan does not undergo cytochrome P-450–mediated biotransformation, its likelihood of drug interactions is minimal.[16]

Among the other ARBs, only telmisartan and losartan have thus far been reported to have potentially significant drug interactions.[11,32,33] Telmisartan increases trough and peak plasma digoxin concentrations by 20% and 49%, respectively.[11] Since a 49% increase in serum digoxin concentration would lead to a supratherapeutic level in a patient with a baseline serum concentration of 1.4 ng/ml (normal range: 0.5 to 2 ng/ml), monitoring is prudent for all patients on digoxin therapy when telmisartan is coadministered.

Losartan undergoes cytochrome P-450 2C9 (CYP2C9) and CYP3A4–mediated biotransformation to active and inactive metabolites.[5,6] One study showed that concurrent administration of losartan and fluconazole, a CYP2C9 inhibitor, reduced the AUC and C_{MAX} of EXP-3174, losartan's active metabolite, by 47% and 30%, respectively.[32] In general, a change exceeding 30% is considered a clinically significant change in AUC.[34] Another study showed that concurrent administration of rifampin (an inducer of CYP1A2, CYP2C, CYP3A4, and UDP glucuronosyl transferase) and losartan resulted in a 40% reduction in the AUC of EXP-3174.[33] Consequently, the possibility of reduced therapeutic effects should be anticipated when losartan is administered simultaneously with rifampin or fluconazole.

Dosing and Administration

Olmesartan doses ranging from 2.5 to 80 mg/day (once daily or divided into two doses) have been evaluated in clinical hypertension trials.[19] Doses of 2.5 mg or greater have been shown to reduce both SBP and DBP to a greater extent than placebo. The dose-response curve appears to plateau at doses ranging from 20 to 40 mg.[20,22] Based on the data from clinical trials, maintenance doses ranging from 5 to 40 mg/day would be reasonable for patients with mild to moderate hypertension, but the lowest dose strength that will be available is 20 mg (personal communication, Sankyo Pharma).

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Antihypertensive Effects of Amlodipine and Hydrochlorothiazide in Elderly Patients With Ambulatory Hypertension

Yves Lacourcière, Luc Poirier, Jean Lefebvre, Françine Archambault, Jean Cléroux, and Guy Boileau

Recent studies and authorities have advocated the use of low-dose thiazide diuretics as first-line treatment agents in elderly hypertensives. However, these recommendations were based solely on blood pressure (BP) measured in the clinic. The objective of the present 32-week double-blind study was to compare the effects of hydrochlorothiazide (HCTZ) and amlodipine (AML) in elderly patients with confirmed ambulatory hypertension. After a 4-week placebo washout period, 42 (25 men, 17 women) patients (mean age, 69 years) with clinic sitting diastolic BP of 95 to 114 mm Hg and daytime ambulatory diastolic BP of ≥90 mm Hg were randomized double-blind to receive AML 5 to 10 mg (n = 21) or HCTZ 12.5 to 25 mg (n = 21) once daily. After 8 weeks of monotherapy, patients in whom clinic diastolic BP remained ≥ 90 mm Hg were given combination therapy with the other agent. Amlodipine monotherapy induced significant reductions in clinic, mean 24-h, daytime and sleep systolic/diastolic BPs whereas only clinic BP decreased significantly in patients treated with HCTZ monotherapy. Moreover, 19/21 versus 8/21 patients on AML and HCTZ monotherapies achieved adequate BP control. At the end of the 32-week treatment period, combination therapy in the HCTZ group resulted in statistically significant reductions in clinic as well as in 24-h, daytime and sleep ambulatory BPs that were similar to those observed in the AML monotherapy group.

In conclusion, the administration of AML monotherapy induced significant reductions in both clinic and ambulatory BPs in elderly patients whereas only clinic BP was significantly decreased by HCTZ monotherapy. Moreover, the addition of AML to HCTZ in patients inadequately controlled by monotherapy has permitted statistically significant decrements in clinic as well as in ambulatory BP. Consequently, the results of the present study suggest that the use of HCTZ in doses of up to 25 mg daily is inadequate for ambulatory BP control in the elderly despite official recommendations. Am J Hypertens 1995;8:1154–1159

KEY WORDS: **Amlodipine, hydrochlorothiazide, elderly ambulatory hypertensives.**

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Thiazide diuretics are now considered to be first-line agents as initial monotherapy for hypertension,[1] especially in elderly patients.[2–4] However, there are presently no data available on the efficacy of smaller doses, that are now recommended,[4,5] in controlling blood pressure (BP) over 24 h in elderly patients with clearly established hypertension.

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Although not promoted as optimal first step in therapy,[1,5] calcium antagonists are extensively used in elderly hypertensive patients. Previous studies have shown that amlodipine, a calcium antagonist of the dihydropyridine class, taken once daily can effectively reduce BP over a full 24-h period.[6,7]

The aim of this study was to compare the antihypertensive efficacy of hydrochlorothiazide with amlodipine, taken once daily, in mild to moderate elderly hypertensive patients. Because casual BP is a rather poor predictor of the daily BP profile,[8] mean ambulatory daytime BP was used to establish the clinical diagnosis of hypertension.[9]

METHODS

Patient Selection Outpatients over 65 years of age with mild to moderate primary hypertension (clinic sitting diastolic BP 95 to 114 mm Hg) in whom all antihypertensive medication was discontinued for at least 4 weeks were candidates for enrollment. Exclusion criteria included coronary heart disease, cerebral disease, significant valvular disease, conduction system disease, atrial fibrillation, renal disease and serum creatinine concentration >135 mmol/L, other significant diseases and patient taking concomitant medication known to affect BP. The protocol and inform consent were approved by Hospital Ethical Review Board.

Protocol After a 4-week single-blind, placebo run-in period, subjects with clinical sitting diastolic BP 95 to 114 mm Hg and mean daytime (from 6 AM to 10 PM) ambulatory diastolic BP ≥90 mm Hg were eligible for the 8-month double-blind treatment. Patients were randomized to receive either 5 mg amlodipine or 12.5 mg hydrochlorothiazide (HCTZ) once daily. After 4 weeks, dosages were increased to 10 mg amlodipine or 25 mg HCTZ once daily to achieve goal sitting diastolic BP of <90 mm Hg. After 8 weeks of double-blind treatment with monotherapy, patients in whom diastolic BP was ≥90 mm Hg began double-blind combination therapy. Those patients at 10 mg amlodipine received amlodipine and 12.5 mg HCTZ once daily during 4 weeks and thereafter 10 mg amlodipine and 25 mg HCTZ if goal BP was not achieved. Patients treated with 25 mg HCTZ received 25 mg HCTZ and 5 mg amlodipine once daily that could be increased to 10 mg after 4 weeks. A fixed dose evaluation period of 20 weeks then ensued during which patients received the dosage established during the titration period.

Clinical Evaluation Before enrollment, patients provided a medical and demographic history and underwent a physical examination, which was repeated at study completion. Conventional BP readings, which were used as the basis for patient entry into the study and for dosage titrations, were obtained in the sitting position after a 15-min rest by a standard mercury sphygmomanometer. Systolic BP was noted when the first Korotkoff sound was heard, and the diastolic BP at the point of disappearance of the fifth Korotkoff sound. Each measurement represented the average of three readings taken 1 min apart. Measurements were obtained immediately before the morning daily dose of medication which was within the interval of 7 and 10 AM, 24 h after the preceding dose.

Ambulatory Blood Pressure Monitoring Twenty-four hour ambulatory BP was measured noninvasively at 15-min intervals between 6 AM and 10 PM and at 30-min intervals between 10 PM and 6 AM using the fully automatic Spacelabs unit 90207 (Montréal, Québec, Canada). Ambulatory BP monitoring occurred three times during the study: at the end of 4-week placebo run-in period, after 8 weeks of monotherapy and at 32 weeks of the double-blind period. Monitor accuracy was validated against a conventional mercury sphygmomanometer using a T-tube connector.[10] The means of three of the clinic and ambulatory diastolic BPs were required to match within ± 5 mm Hg. The medication was then administered by a pharmacist. On the day that the monitoring was completed, dubious readings were edited out for further analysis. The following quality control criteria were established as standards for acceptability for each ambulatory BP monitoring report: 1) a minimum of 24 h of data postdose; 2) a minimum of 64 total valid readings (80% of total readings); 3) a minimum of 22 total valid reading hours; and 4) no two consecutive invalid hours.

STATISTICAL ANALYSIS

The analysis of demographic data was made with a one-way analysis of variance (ANOVA). For each treatment group, a one-way ANOVA for repeated measures was used to compare mean changes from baseline for BP and heart rate. The significance of change in BP and heart rate from baseline or the difference between treatment groups was determined by analysis of covariance (ANCOVA) using baseline data as the covariates. Data are given as mean ± SE. A $P < .05$ was accepted as significant.

RESULTS

A total of 51 white patients entered the study: nine (18%) patients were subsequently excluded after the placebo run-in period because they did not fulfill ambulatory BP criteria for randomization. A total of 21 patients were randomized to amlodipine and 20 to HCTZ; all patients completed the study and had three periods of ambulatory BP monitoring. No significant differences were noted between the amlo-

dipine and HCTZ groups in terms of sex, age, body weight, height, duration of hypertension or BP (Table 1). At the end of this study, 19 patients (90%) from the amlodipine group were taking amlodipine monotherapy while two patients were on amlodipine plus the diuretic. The HCTZ group included eight patients (38%) on monotherapy and 13 patients taking the combination with amlodipine. In both groups weight remained stable during the study.

Effects on Clinic Blood Pressure and Heart Rate The efficacy analysis was based on measurements made 24 h postdose at the end of the placebo period, after 8 weeks of monotherapy and at the end of the double-blind treatment. Mean changes in clinic BP and heart rate are shown in Table 2. After 8 weeks of double-blind treatment, the amlodipine group had greater reduction in sitting systolic and diastolic BP than the HCTZ group with monotherapy but the difference between groups did not reach significance. Blood pressure did not decrease further after 8 months of treatment in the amlodipine group. In contrast, the combination therapy induced additional BP reduction in the HCTZ group, which was comparable to that achieved in the amlodipine group. Normalization rates (sitting diastolic BP < 90 mm Hg) were 90% for amlodipine and 38% for HCTZ as monotherapies. After the addition of amlodipine, the normalization rate increased to 76% in the HCTZ group, while it remained unchanged in the amlodipine group when the combination was given. There were no significant changes in heart rate in either group with mean sitting values at weeks 8 and 32 being almost identical to baseline readings.

Effects on Ambulatory Blood Pressure The mean ambulatory 24-h, daytime and nighttime BP produced by amlodipine and HCTZ as single drugs or in combination are presented in Table 3. Blood pressure was significantly reduced after 8 weeks by amlodipine monotherapy, but not by HCTZ for each of the 24-h periods. Moreover, there were statistically significant differences in 24-h, daytime and nighttime diastolic BP between amlodipine and HCTZ groups. While BP remained virtually unchanged in the amlodipine groups from 2 to 8 months of treatment, the addition of amlodipine produced significant decreases in both systolic and diastolic BP for each of the periods in the HCTZ group. At the end of the study, BP reduction was comparable in both groups of patients. The mean hourly ambulatory BP for all the amlodipine and HCTZ-treated patients are illustrated in Figures 1 and 2. Ambulatory monitoring showed that amlodipine monotherapy reduced systolic and diastolic BP every hour of the circadian cycle (Figure 1). In contrast similar BP reduction was noticeable in the HCTZ group only when amlodipine was added to the diuretic (Figure 2). Mean heart rate was not significantly reduced with either treatment during ambulatory recordings.

TABLE 1. PATIENT DEMOGRAPHIC DATA AT BASELINE

	Amlodipine	Hydrochlorothiazide
No. of patients	21	21
Sex (male/female)	12/9	13/8
Age (years)	69 ± 1	69 ± 1
Weight (kg)	77 ± 4	78 ± 3
Height (cm)	164 ± 2	165 ± 2
Duration of hypertension (years)	14 ± 2	16 ± 2
Average blood pressure (mm Hg)	167 ± 4/99 ± 1	167 ± 4/101 ± 1

Evaluation of the 24-Hour Efficacy by Trough/Peak Ratio In order to further demonstrate the duration of action of amlodipine and HCTZ monotherapies, adjusted mean decrements in systolic and diastolic ambulatory BP at peak activity and at trough activity (24-h postdose) were calculated after subtracting the placebo effect.[11] They were used for assessing the trough/peak (t/p) ratios. After 8 weeks of treatment, amlodipine induced a sustained effect throughout the 24-hour interval, exibiting ratios of 61% and 63% for systolic and diastolic BPs respectively. In contrast, HCTZ produced inadequate t/p ratios on ambulatory systolic (32%) and diastolic (33%) BP, suggesting that the low magnitude of effect was even greater at the end of the 24-h interval.

Symptoms and Side Effects All patients randomized to active medication were included in the evaluation of adverse effects. A total of 41 adverse events was reported during treatment with monotherapy, 21 by patients taking amlodipine and 20 by those taking HCTZ. Ankle edema was the most frequently reported symptom with amlodipine (four patients), whereas three patients treated with HCTZ reported fatigue. The combination therapy did not increase the number of adverse events in either group. The severity of most complaints were reported as mild or moderate.

DISCUSSION

Our analyses demonstrate that while amlodipine monotherapy induced significant reduction in clinic and ambulatory BP in every one of the 24-h periods, BP was significantly reduced only in the clinic for the HCTZ group. Moreover, the addition of amlodipine in patients treated with HCTZ not only increased the percentage of normalization rate, but resulted in ambulatory BP control. In addition, the t/p ratios and the

TABLE 2. EFFECTS OF ANTIHYPERTENSIVE TREATMENT ON CLINIC BLOOD PRESSURE

	Amlodipine (n = 21)			Hydrochlorothiazide (n = 21)		
Parameter	Baseline	8 weeks	32 weeks†	Baseline	8 weeks	32 weeks†
SBP (mm Hg)	167 ± 4	149 ± 3***	148 ± 3***	167 ± 4	156 ± 3*	146 ± 3****
DBP (mm Hg)	99 ± 1	83 ± 1****	85 ± 1****	101 ± 1	95 ± 2*	88 ± 1****
HR (beats/min)	80 ± 2	77 ± 2	75 ± 2	72 ± 2	76 ± 2	76 ± 2

SBP = Systolic blood pressure, DBP = Diastolic blood pressure, HR = Heart rate

*p < .05, ***p < .001, ****p < .0001 versus baseline values*

†Combination therapy in 2/21 (10%) and 13/21 (62%) patients of the amlodipine and hydrochlorothiazide, respectively.

hourly BP profiles reveal that only amlodipine was effective for 24 h.

Thiazide diuretics are the only antihypertensives that have been extensively studied in large scale clinical trials and which have been consistently shown to reduce cerebrovascular morbidity and mortality and (to a lesser extent) death from coronary heart disease in the elderly hypertensive patients.[2–4] Although they are not considered to be "preferred" treatment for most hypertensive patients,[12] thiazide diuretics in low dosages (12.5 to 25 mg per day) are now recommended by the JNC-V[1] and other authorities[5] as the first line therapy for the treatment of hypertension in older people.

A surprising finding in the present study, which differed from most other studies[2–4] is that target clinic pressure was reached by HCTZ monotherapy only in 38% of the subjects. Although the results are affirmative, some limitations in our study design should be considered. First, it is possible that increasing the thiazide dosage above 25 mg would have produced the desired reduction in BP in a larger proportion of patients, as demonstrated by Materson et al.[13] Such increase was not done as the goal of the present study was to evaluate the antihypertensive efficacy of the actual recommended dosages of HCTZ.[1,5] Moreover, the use of dosages higher than 25 mg may cause deleterious metabolic side effects.[13] Second, no effort was made to restrict dietary NaCl in our patients. Therefore, some of the antihypertensive effect of HCTZ could have been missed. However, since none of the subjects had serum creatinine >135μmol/L or evidence of renal impairment, it is unlikely that major differences in BP lowering effect were lost.[14]

To date, no trials have reported on the antihypertensive efficacy of low dose thiazide diuretics in el-

TABLE 3. EFFECTS OF ANTIHYPERTENSIVE TREATMENT ON AMBULATORY BLOOD PRESSURE

Variable	Treatment Group	Baseline	8 weeks	32 weeks‡
Whole day				
SBP	Amlodipine	157 ± 3	143 ± 3**	141 ± 3***
	Hydrochlorothiazide	154 ± 4	149 ± 3^{NS}	135 ± 3****
DBP	Amlodipine	89 ± 2	79 ± 1***††	79 ± 1***
	Hydrochlorothiazide	89 ± 2	87 ± 2^{NS}	79 ± 2***
Daytime (6AM–10PM)				
SBP	Amlodipine	161 ± 3	146 ± 3**	144 ± 3**
	Hydrochlorothiazide	157 ± 3	153 ± 3^{NS}	138 ± 3***
DBP	Amlodipine	97 ± 2	88 ± 1***††	88 ± 1***
	Hydrochlorothiazide	99 ± 2	97 ± 2^{NS}	88 ± 2***
Nighttime (10PM–6AM)				
SBP	Amlodipine	150 ± 4	136 ± 3**	135 ± 3**
	Hydrochlorothiazide	147 ± 5	142 ± 4^{NS}	129 ± 4**
DBP	Amlodipine	81 ± 2	74 ± 2**†	74 ± 1**
	Hydrochlorothiazide	83 ± 3	80 ± 2^{NS}	73 ± 2**

SBP = Systolic blood pressure; DBP = Diastolic blood pressure.

*P < .05, **P < .01; ***P < .001; ****P < .0001 versus baseline values.*

†P < .05; ††P < .001 versus hydrochlorothiazide.

‡Combination therapy in 2/21 (10%) and 13/21 (62%) patients of the amlodipine and hydrochlorothiazide, respectively.

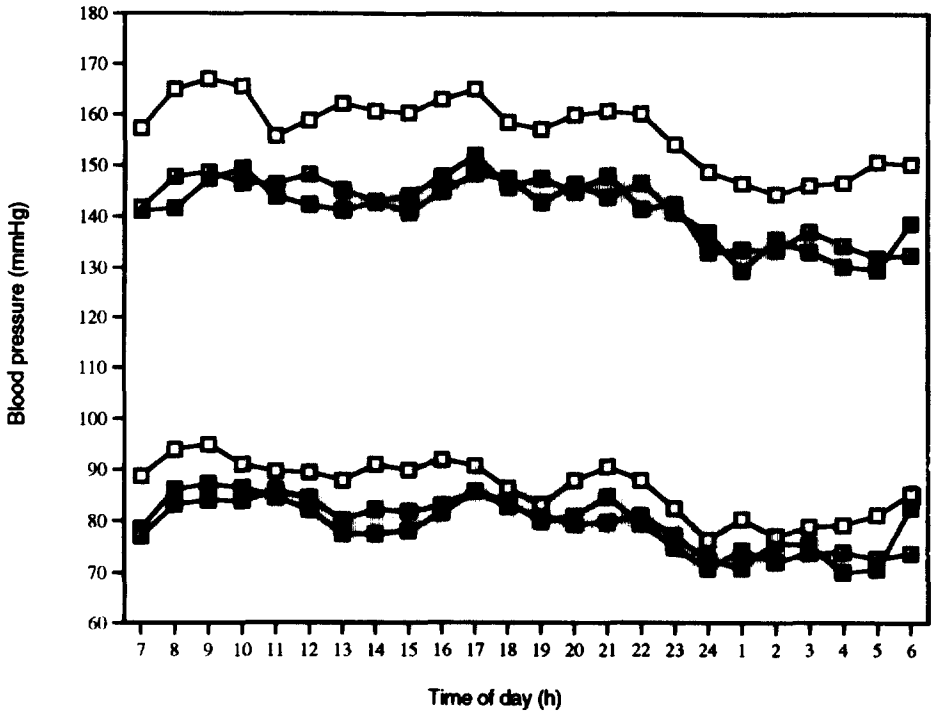

FIGURE 1. *Mean hourly systolic and diastolic blood pressure at baseline (□) and during treatment with amlodipine monotherapy (◪) or in combination with hydrochlorothiazide (■).*

derly patients with hypertension documented by ambulatory BP monitoring. The inclusion of nonconfirmed hypertensive patients in previous major clinical trials in the elderly patients has two major implications. First, a significant number of white coat hypertensives could have been included in the studies as white coat syndrome has been reported to be common in patients over the age of 65 with an estimated prevalence of 42% to 46% of hypertensives.[15,16] These numbers may be relevant because cardiovascular morbidity has been shown to be lower in white coat hypertensives than in those with ambulatory hypertension and not dissimilar to that observed in normotensive patients.[17] Second, the inclusion of white coat hypertensives in these trials might have caused a meaningful negative impact on the

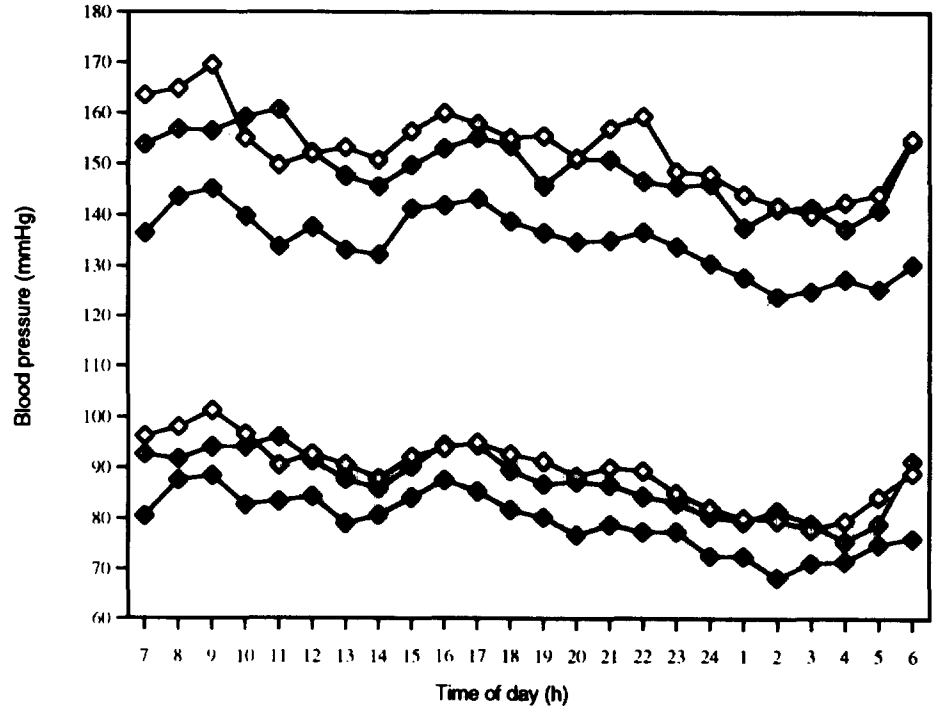

FIGURE 2. *Mean hourly systolic and diastolic blood pressure at baseline (◇) and during treatment with hydrochlorothiazide monotherapy (◈) or in combination with amlodipine (◆).*

quantification of BP response to antihypertensive therapy.[18–20] In fact a diluting effect may have resulted from their inclusion in the studies as the medications lower clinic pressure without affecting ambulatory BP.

There is limited information concerning the long-term effects of calcium channel blockers or angiotensin converting enzyme inhibitors on cardiovascular endpoints. The results of the present study showing that the calcium antagonist amlodipine as opposed to HCTZ controlled ambulatory BP may be relevant as ambulatory BP has recently been shown to be an independent predictor of cardiovascular risks.[16] Additional long-term studies are, however, required to establish the superiority of these newer antihypertensive agents in elderly patients with confirmed ambulatory hypertension who are at greater risk of cardiovascular events.[16]

We conclude that administration of the calcium antagonist amlodipine produces a sustained reduction of clinic and ambulatory BPs in elderly patients with confirmed hypertension whereas only clinic BP is significantly reduced by low doses of HCTZ. Therefore, our results are not in agreement with the official consensus recommendations and suggest that the use of HCTZ in doses up to 25 mg daily does not control BP in elderly hypertensive patients, especially those with elevated ambulatory BP.

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Head-to-Head Comparisons of Hydrochlorothiazide With Indapamide and Chlorthalidone

Antihypertensive and Metabolic Effects

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See Editorial Commentary, pp 983–984

Abstract—Hydrochlorothiazide (HCTZ) has often been contrasted with chlorthalidone, but relatively little is known about HCTZ versus indapamide (INDAP). This systematic review retrieved 9765 publications, and from these, it identified 14 randomized trials with 883 patients comparing HCTZ with INDAP and chlorthalidone on antihypertensive potency or metabolic effects. To make fair comparisons, the dose of the diuretic in each arm was assigned 1 of 3 dose levels. In random effects meta-analysis, INDAP and chlorthalidone lowered systolic blood pressure more than HCTZ: −5.1 mm Hg (95% confidence interval, −8.7 to −1.6); *P*=0.004 and −3.6 mm Hg (95% confidence interval, −7.3 to 0.0); *P*=0.052, respectively. For both comparisons, there was minimal heterogeneity in effect across trials and no evidence for publication bias. The HCTZ–INDAP contrast was biased in favor of greater HCTZ potency because of a much greater contribution to the overall effect from trials in which the HCTZ arm had a higher dose level than the INDAP arm. For the HCTZ–INDAP comparison, no single trial was responsible for the overall result nor was it possible to detect significant modifications of this comparison by duration of follow-up, high- versus low-bias trials, or the presence or absence of background medications. There were no detectable differences between HCTZ and INDAP in metabolic adverse effects, including effects on serum potassium. In conclusion, these head-to-head comparisons demonstrate that, like chlorthalidone, INDAP is more potent than HCTZ at commonly prescribed doses without evidence for greater adverse metabolic effects. **(*Hypertension*. 2015;65:1041-1046. DOI: 10.1161/HYPERTENSIONAHA.114.05021.)** • **Online Data Supplement**

Key Words: blood pressure ■ chlorthalidone ■ hydrochlorothiazide ■ hypokalemia ■ indapamide

Recommended as first line agents in most hypertension guidelines,[1,2] thiazide-related diuretics are particularly useful in resistant and salt-sensitive forms of hypertension, the latter group accounting for half of all hypertension, including black, elderly, obese, and diabetic patients.[3,4] However, not all thiazide-related medications have the same properties, and many studies have contrasted the most widely used thiazide diuretic, hydrochlorothiazide (HCTZ), and the thiazide-like diuretic, chlorthalidone (CTDN), with respect to duration of action, antihypertensive potency, nonblood pressure–related pleiotropic features, reduction of left ventricular hypertrophy, and reduction of cardiovascular events.[5] These studies have been accompanied by many helpful commentaries contrasting the 2 medications. However, relatively little is known as to how HCTZ compares with another thiazide-like medication, indapamide (INDAP), even though both INDAP and CTDN have been recommended in place of HCTZ.[6] Therefore, we conducted a systematic review and meta-analysis of head-to-head randomized controlled trials to address this question. In addition, head-to-head trials contrasting HCTZ with CTDN were analyzed to further quantify the relative potency of those 2 drugs and to place the HCTZ–INDAP comparisons in context.

Methods

This review and analysis followed recommended guidelines.[7] Using each of the 3 diuretics as keywords, we searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials with both narrow and broad searches (Figure S1 in the online-only Data Supplement for further details). General inclusion criteria were randomized trials of hypertensives reported in English with systolic blood pressure (SBP), metabolic parameters, or cardiovascular events as outcomes and contrasting 2 or 3 of the diuretics (HCTZ, CTDN, and INDAP) with one another. For trials limited to antihypertensive and metabolic effects as outcomes, exclusion criteria were BP limited

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to standing BP only, drug dose titrated to effect on the outcome; follow-up <2 weeks; and follow-up >6 months (because such trials are likely to be focused on other outcomes and therefore might measure blood pressure less rigorously). Sitting BP was chosen over supine BP where both were given. Trials were limited to diuretics at commonly prescribed doses (online-only Data Supplement).

To make fair comparisons between drugs, the diuretic dose in milligrams in each arm was classified according to 3 dose levels (or steps) using 10 different sources (Section 1 and Table S1 in the online-only Data Supplement): HCTZ: 12.5, 25, and 50; CTDN: 6.25, 12.5, and 25; INDAP immediate-release: 1.25, 2.5, and 5; INDAP sustained release: 1.5, 2.0, and 2.5. Each trial was then classified by relative dose level: HCTZ higher (HCTZ dose higher than INDAP or CTDN dose), INDAP higher (INDAP dose higher than HCTZ dose), CTDN higher (CTDN dose higher than HCTZ dose), and dose equivalent (drugs given at the same dose in the 2 arms).

Data analyzed were mean effect, SD, and number of patients, n, in each arm. Where necessary, the SD was computed as SE times $n^{1/2}$. Ninety-five percent confidence intervals (95% CI) were obtained by pooling the variances of each arm. For the overall effect, variances of confidence limits for all trials were pooled. Random effects meta-analysis was used throughout. The DerSimonian–Laird model was used initially, supplemented by the more conservative Knapp–Hartung model where appropriate.

Sensitivity analyses were (1) a leave-one-trial-out analysis, (2) analysis of low- versus high-bias trials, (3) analysis of trials with background versus no background drug, (4) analysis with follow-up >4 weeks versus ≤4 weeks, (5) use of a 2-level classification for INDAP (1.25/2.5) rather than the 3-level classification (1.25/2.5/5), (6) use of the single most precise study,[8] (7) use of the 3 largest studies,[8] and (8) analyses for publication bias using funnel plots and testing by the Duval–Tweedie method. All analyses used Comprehensive Meta-Analysis software, version 3.2.00089 (March 24, 2014).

Results

The search yielded 9765 references (Figure S1) of which were 14 eligible trials: 10 with HCTZ–INDAP comparisons of SBP, 3 with HCTZ–CTDN comparisons of SBP, and 9 with HCTZ–INDAP comparisons of metabolic parameters (Table 1).[9–22] No trials compared CTDN with INDAP, and all trials lacked cardiovascular events as outcomes. Contrasting CTDN with HCTZ on metabolic effects was lacking. Table 1 shows baseline characteristics. One HCTZ–INDAP comparison lacked information on SDs and attempts to reach its authors were unsuccessful;[23] including this trial would have favored INDAP compared with HCTZ with respect to antihypertensive effect. Seven trials were double blind. Table S2 gives the 4 other data quality characteristics.

Table 1. Characteristics of Trials Comparing HCTZ With INDAP and HCTZ With CTDN

Authors	Number, Baseline SBP	Baseline Comorbidities When Specified	HCTZ and INDAP Dose or HCTZ and CTDN Dose	Relative Dosage	Weeks of Follow-Up
HCTZ versus INDAP					
Bhigjee et al[9] (black patients)*	19, NR†,‡	No CVD, no DM	25 and 2.5	Equivalent	4
Bhigjee et al[9] (Indian patients)*	18, NR†,‡	No CVD, no DM	25 and 2.5	Equivalent	4
Elliott et al[10]*	11, 168‡	Serum uric acid >8 mg/dL, no CKD	25 and 2.5	Equivalent	4
Emeriau et al[11]	524, 175	(Age 65+) No CAD, no symptomatic CHF, no CKD	25 and 1.5 SR	HCTZ>INDAP	12
Kreeft et al[12]*	17, 151‡	No CVD or DM	50 and 2.5	HCTZ>INDAP	12
Krum et al[13]*	18, 141	All with DM	12.5 and 2.5§	INDAP>HCTZ	8
Madkour et al[14]	28, 167	All had CKD	50 and 2.5	HCTZ>INDAP	12
Malini et al[15]*	31, 165	Uncomplicated hypertension (all on enalapril at baseline)	25 and 2.5¶	Equivalent	12
Plante et al[16]	24, 137	Not reported	50 and 2.5	HCTZ>INDAP	12
Plante et al[17]*	42, 183	Age 65+	50 and 2.5	HCTZ>INDAP	2
Radevski et al[18]*	42, 149‡	Excludes insulin-dependent DM	12.5 and 2.5	INDAP>HCTZ	12
Spence et al[19]*	39, 150	No angina, CHF, aortic stenosis, or DM	25 and 2.5	Equivalent	26
HCTZ versus CTDN					
Ernst et al[20]	24, 142	No MI or stroke in the previous 6 mo	50 and 25	Equivalent	8
Pareek et al[22]	18, 154‡	No CVD, no DM	12.5 and 6.25	Equivalent	4
Kwon et al[21]	28, 152	No CHF	25 and 12.5	Equivalent	8

CAD indicates coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; CTDN, chlorthalidone; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; HCTZ, hydrochlorothiazide; INDAP, indapamide; MI, myocardial infarction; NA, not available; SBP, systolic blood pressure, and SR, sustained release.

*Includes data on metabolic measurements.

†Not relevant. Trial used only for metabolic outcomes.

‡Crossover trial.

§Both medications added to 20 mg of fosinopril.

¶Both medications added to 20 mg of enalapril.

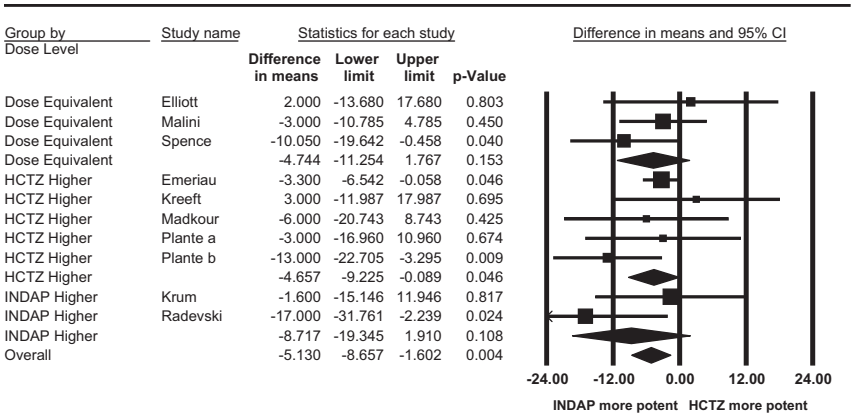

Figure 1. For systolic blood pressure, random effects, DerSimonian–Laired meta-analysis comparing hydrochlorothiazide (HCTZ) and indapamide (INDAP). The Knapp–Hartung model gave −4.7 (−8.0 to −1.4), P=0.010. τ=1.2 versus an overall effect of 5.1 and I^2=6%, indicating minimal heterogeneity. HCTZ-higher trials weighted the overall effect by 69% compared with 8% from INDAP-higher trials, a bias favoring HCTZ. CI indicates confidence interval.

Relative to HCTZ, INDAP produced a greater reduction in SBP: −5.1 mm Hg (95% CI, −8.7 to −1.6), P=0.004 (Figure 1). There was minimal heterogeneity across the 10 trials. Because of substantial differences in dose levels for the 2 drugs, the result was biased in favor of HCTZ having a greater potency than INDAP (description in Figure 1 and Table S3). INDAP and HCTZ were not detectably different in their effects on serum potassium (Figure 2). Relative differences in other metabolic effects are shown in Table 2. As with potassium, there were no detectable differences between HCTZ and INDAP for these metabolic effects.

Results for sensitivity analyses are as follows: (1) the overall results were not dependent on any 1 trial (Figure S2a). (2) For SBP reduction, there was no statistically significant interaction between the INDAP–HCTZ effect and the following: (a) trials with low versus high bias (Figure S2b), (b) trials with nondiuretic background medications versus trials without such drugs (SBP reductions were −2.6 [−10.0 to 4.8] and −5.5 [−9.1 to −1.9], respectively, P=0.500 for interaction; there were only 2 trials with background medications, so statistical power was limited.), and (c) trials with short (≤4 weeks) versus long (>4 weeks) follow-up (SBP reductions were −8.8 [−17.2 to −0.4] and −4.2 [−7.1 to −1.3], respectively, P value=0.315 for interaction). (3) Using a 2-level classification for INDAP dose (1.25/2.5) rather than the 3-level classification (1.25/2.5/5) led to a weight of 84% from trials with the HCTZ dose being higher than the INDAP dose and 16% from trials with the HCTZ dose being lower than the INDAP dose. (4) There was no detectable publication bias with identical observed and adjusted differences in BP potency between the 2 drugs (Figure S3a). (5) The trial with the smallest SE gave a reduction in SBP by INDAP versus HCTZ of −3.3 (−6.5 to −0.1) (Figure 1).[11] (6) The 3 largest trials showed a mean SBP reduction of −6.4 (−11.1 to −1.7).[11,17,18]

Contrasting HCTZ with CTDN also showed a greater reduction in SBP from CTDN compared with HCTZ: −3.6 (95% CI, −7.3 to 0.0), P=0.052 (Figure 3). The trial with the narrowest SE (and also the largest number) showed a difference of −2.5 (−6.9 to 1.89). The trial with the highest quality had the greatest reduction in SBP by CTDN relative to HCTZ: −6.3 (−16.3 to 3.7). There was again no evidence for publication bias for this comparison (Figure S3b).

Discussion

These head-to-head comparisons demonstrate that, at commonly used doses, INDAP lowers SBP more than HCTZ without evidence for greater adverse effects. There was also evidence (although limited to fewer patients) that CTDN was more potent than HCTZ. Compared with an estimated 9.5-mm Hg reduction in SBP from HCTZ relative to placebo from Peterzan et al,[24] INDAP and CTDN lowered SBP by 54% and 38% more than HCTZ, respectively. The advantage in antihypertensive potency of INDAP compared with HCTZ was probably underestimated because of the much greater weight on the overall effect from trials in which HCTZ was given at a higher dose level than INDAP. This HCTZ–CTDN head-to-head synthesis is consistent with the masterful but indirect comparisons of previous meta-analyses.[24,25] The present

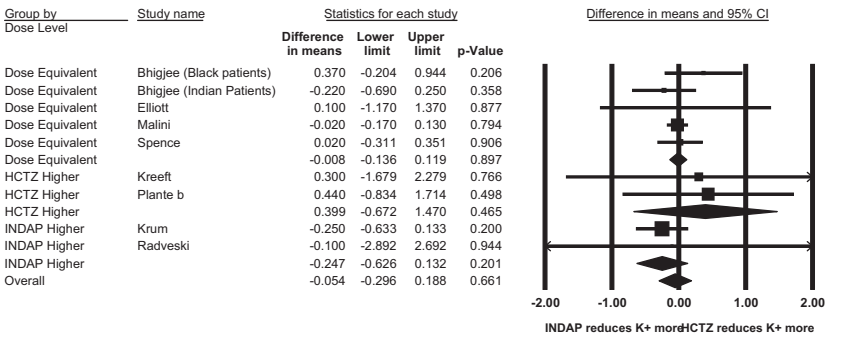

Figure 2. For the effects on serum potassium in mEq/L, random effects, DerSimonian–Laired meta-analysis comparing hydrochlorothiazide (HCTZ) and indapamide (INDAP). There was no heterogeneity across trials. HCTZ-higher trials weighted the overall effect by 1% compared with 10% from INDAP-higher trials, indicating a slight bias toward INDAP causing a greater hypokalemic effect. CI indicates confidence interval.

Table 2. Trends for Adverse Metabolic Effects From HCTZ Compared With INDAP With Change (95% Confidence Intervals)

Adverse Effect	Change From INDAP Minus Change From HCTZ	Units
Low potassium	−0.1 (−0.3 to 0.2)	mEq/L
Low sodium	1 (−1 to 3)	mEq/L
High creatinine	0.1 (−0.1 to 0.2)	mg/dL
High glucose	4 (−3 to 11)	mg/dL
High cholesterol	−5 (−17 to 7)	mg/dL
High uric acid	−0.2 (−0.7 to 0.4)	mg/dL

HCTZ indicates hydrochlorothiazide; and INDAP indapamide.

HCTZ–INDAP head-to-head findings have apparently not been reported previously.

Although these studies lacked cardiovascular events as outcomes, there are other relevant data. INDAP has reduced left ventricular mass index by 17% ($P<0.001$), whereas HCTZ had no significant effect on this end-organ process.[26] INDAP's reduction of left ventricular hypertrophy has been repeatedly demonstrated and is more pronounced than that of enalapril.[27] Furthermore, INDAP was found to be comparable with captopril and enalapril in reducing albuminuria in diabetes mellitus,[28] whereas in another study, HCTZ had no effect on this pathology.[29] Compared with HCTZ, INDAP is more effective in scavenging oxygen radicals and in inhibiting platelet aggregation.[30,31]

For reducing cardiovascular events, in the PATS (Post Stroke Antihypertensive Treatment Study) trial, 2.5 mg of INDAP reduced stroke by 29% and all cardiovascular events by 23% versus placebo.[32] In the PROGRESS (Preventing Strokes by Lowering Blood Pressure in Patients With Cerebral Ischemia) trial, only when INDAP was added to perindopril was there a reduction in risk of stroke.[33] The perindopril–INDAP combination also reduced cardiovascular events in 2 other placebo-controlled trials.[34,35] In contrast, in the Oslo study, compared with an untreated control group, the HCTZ arm (65% of whose patients were on one or more additional antihypertensives) significantly reduced the risk of stroke but not coronary artery disease or all cardiovascular events combined.[36] HCTZ was inferior to enalapril and amlodipine in head-to-head trials and inferior to CTDN in network analysis.[5]

Although HCTZ has less than a 24-hour duration of diuretic and antihypertensive action,[5,20] the duration of antihypertensive action for INDAP immediate-release and INDAP sustained release is estimated as 24+ hours and 32+ hours, respectively.[37] This is important because targeting night-time BP may reduce cardiovascular events more than targeting daytime BP.[38–40]

In spite of greater antihypertensive potency, INDAP did not have a detectably greater effect than HCTZ on metabolic adverse effects. Findings regarding serum potassium are consistent with previous studies showing declines in serum potassium from INDAP immediate-release 2.5 mg of −0.30 to −0.42 mEq/L,[41,42] similar to the decline found with HCTZ 25 mg.[24,25] Unlike HCTZ, INDAP has no effect on serum lipids.[43]

Initially, thiazide-related diuretics lower BP via diuretic effects, but ultimately, their antihypertensive effects stem from decreased peripheral arterial resistance through unknown mechanisms.[3] In contrast, INDAP is known to also operate via a direct vasodilator effect from inhibitory activity against vasopressors and decreased inward flow of calcium ions in vascular smooth muscle.[44] Consistent with this mechanism, INDAP reduces BP in end-stage renal disease, unlike HCTZ.[45]

At 2.5 mg per day, INDAP has been described as a weak diuretic. However, its natriuretic and aquaretic effects are dose related. Doubling the dose to 5 milligrams daily promotes volume loss, similar to the effect of 40 mg of furosemide.[46] Thus, at the 5-mg dose, INDAP would address the salt and volume excess of resistant hypertension (as well as provide optimal antihypertensive potency) and would also be a useful diuretic for salt-sensitive hypertension.

Limitations of this study include the wide CIs reflecting some limitations in statistical power, the absence of 24-hour blood pressure measurements (which are better predictors of cardiovascular events), and the absence of cardiovascular events as outcomes. Also, half of the weight for the HCTZ–INDAP comparison came from 1 trial.[11] In addition, these results must be properly interpreted: this analysis does not demonstrate that INDAP is more efficacious than HCTZ for reducing SBP (ie, that INDAP's superiority is maintained when the 2 drugs are given at high doses). Strengths of this study are the head-to-head rather than indirect comparisons, the consistency of effects (ie, the relatively small values for τ and I^2 in Figure 1), the verification of the results by the several sensitivity analyses, and the lack of evidence for publication bias. Removing the trial contributing half of the weight to the HCTZ–INDAP comparison leads to a result even more in favor of INDAP: SBP reduction of −6.1 (95% CI, −10.1 to −2.1). Although this analysis does not show that CTDN is more efficacious than HCTZ, this synthesis does show that INDAP is more potent than HCTZ at commonly prescribed dose levels.

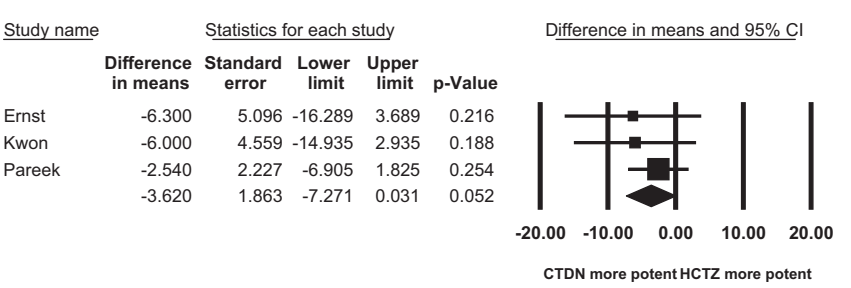

Figure 3. Meta-analysis for systolic blood pressure reduction comparing hydrochlorothiazide (HCTZ) and chlorthalidone (CTDN). $\tau=0$ and $I^2=0\%$, indicating no detectable heterogeneity across trials and no need for the Knapp–Hartung model. CI indicates confidence interval.

Perspectives

In 2013 in the United States, there were 50 million prescriptions for HCTZ making this the 12th most commonly prescribed drug.[47] However, HCTZ has lesser antihypertensive potency as shown here and has several other types of deficiencies.[5] CTDN is generally offered as the alternative, and the present results, based on head-to-head trials, confirm CTDN's superiority reported from indirect HCTZ–CTDN comparisons. However, in countries such as the United States, clinicians may avoid CTDN because it has only 1 unscored dose preparation, which is at the maximum recommended dose, making it an impractical choice for many patients. In contrast, INDAP has low and intermediate dose formulations and, in Europe, is also available in slow release, thus giving it much greater flexibility than CTDN. Like CTDN ($19 per month), INDAP immediate-release is relatively inexpensive at $4 per month. Although US guidelines for the management of resistant hypertension advocate CTDN,[3] this analysis implies that INDAP should also be preferred compared with HCTZ for this condition. In addition, these results support the view that CTDN and INDAP are preferable to HCTZ for managing hypertension in general.

Disclosures

None.

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Novelty and Significance

What Is New?

- This study synthesizes trials on the relative potency of hydrochlorothiazide (HCTZ) and indapamide for the first time.
- Although indirect comparisons have compared HCTZ and chlorthalidone with respect to antihypertensive potency, this synthesis is the first to compare head-to-head randomized trials.

What Is Relevant?

- HCTZ is the 12th most commonly prescribed drug in the United States, with 50 million prescriptions annually for monotherapy alone.
- Chlorthalidone is commonly cited as the alternative to HCTZ; this analysis confirms chlorthalidone's superior antihypertensive potency.
- This study demonstrates for the first time that indapamide is ≈50% more potent than HCTZ.
- In countries such as the United States, chlorthalidone has only 1 dosage form, an unscored, maximum dose tablet. Because indapamide has ≥2 dosage forms in the low-to-intermediate dose range, it is a more appropriate alternative to HCTZ in many instances.
- These features apply to resistant hypertension and to the treatment of hypertension in general.

Summary

Based on an analysis of head-to-head trials, indapamide and chlorthalidone are more potent than HCTZ in lowering systolic blood pressure.

ONLINE SUPPLEMENT

Clinics, Head-to-Head Comparisons of Hydrochlorothiazide with Indapamide and Chlorthalidone: Antihypertensive and Metabolic Effects

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January 23, 2015

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Running title: Potency of HCTZ, Indapamide and Chlorthalidone

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FILE SUPPLEMENT

Section 1. Classification of dose levels: Text and Table S1.

The dose levels are based on the following 10 sources: randomized trials (7 in number); the hypertension guidelines from JNC 8, the American Society of Hypertension, and the International Society of Hypertension; 2 textbooks (one published by the American Heart Association and another authored by 2 hypertension specialists); a popular evidence based reference for physicians; a widely used mobile application for physicians; review articles (8 in number), and dosage forms identified by 3 different sources.

HCTZ: 12.5 / 25/ 50. All sources support this 3 level classification.

INDAP IR: 1.25/ 2.5/ 5. This was supported by 4 out of the 9 sources, 2 of which were commonly used physician references (UpToDate and Epocrates mobile), as well as by 4 studies of dosage,[13,14] including the fact that INDAP has a substantially stronger diuretic effect at 5 mg than at 2.5 mg.[15] The alternative would be a 2 level classification (1.25/2.5). This issue was examined and reported in the RESULTS section as a sensitivity analysis.

INDAP SR: 1.5/ 2/ 2.5. This was consistent with the 3 dosage forms and with the following: (1) The mean systolic BP lowering for indapamide IR 2.5 and indapamide SR 2 are virtually identical being within 0.1 mmHg of each other.[4] (2) Combining data from two reports shows that indapamide IR 2.5 is about 20% more potent than indapamide SR 1.5 although confidence limits were wide.[16,17] This implies that indapamide SR 1.5 is at a lower dose level than indapamide IR 2.5, particularly if one considers that doubling the dose of an antihypertensive produces only a 22% increase in potency.[18]

CTDN: 6.25/ 12.5/ 25. One might replace the 1st and 3rd level assignments of 6.25 and 25, respectively, with, for example, 12.5 and 50, or possibly just 2 dosage levels, 12.5 and 25. At the low end, our assignment of 6.25 is warranted by the recognition among many physicians that a starting dose of 12.5 might be too high for frail or elderly patients, and this viewpoint is reflected in the presence of 6.25 mg formulations stand alone and in fixed dose preparations in India and a 12.5 mg tablet that is scored in Venezuela. At the high dose end of the spectrum, CTDN at 12.5-25 mg in ALLHAT reduced cardiovascular events equal to or greater than the reductions from each of the 3 comparator drugs (lisinopril, amlodipine, and doxazosin) while producing a worrisome 8% prevalence of hypokalemia (ALLHAT 2002) and suggesting to many clinicians that CTDN doses above 25 mg are unnecessarily risky. These classifications are also consistent with a prior meta-analysis of HCTZ and CTDN (Peterzan 2012).

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Table S1. Dose range in milligrams for hydrochlorothiaizide, chlorthalidone, and indapamide from randomized trials, hypertension guidelines, textbooks, physician references, and dosage forms used for the 3 level classifications in this analysis.

Antihypertensive	**HCTZ**	**INDAP IR**	**INDAP SR**	**CTDN**
Doses used in randomized trials with cardiovascular events as outcomes*	12.5, 25: ACCOMPLISH 2008 50: Oslo 1980[5,6]	2.5: PATS 1995[7]		12.5, 25: SHELL 2003; ALLHAT 2002; SHEP 1992 25-100: HDFP 1979[8-11]
Doses used in research or review articles with blood pressure as the outcome (see text)		5 mg as the maximum dose	1.25/ 2/ 2.5	6.25 / 12.5/ 25 for CTDN roughly equipotent with 12.5/ 25/ 50 for HCTZ[12]
JNC8 2014[1]	12.5-50	1.25-2.5		12.5-25
American Society of Hypertension[2]	12.5-50	1.25-2.5		12.5-25
International Society of Hypertension[2]	12.5-50	1.25-2.5		12.5-25
Hypertension Primer 2008 (AHA)[3]	12.5-50	1.25-5		12.5-50
Clinical Hypertension 2010[4]	12.5-50	1.25-5		12.5-50
UpToDate (Lexicomp) 2014	12.5-50	1.25-5		12.5-100
Epocrates Mobile 2014	12.5-50	1.25-5		12.5-100
Dosage forms[6]	12.5/ 25/ 50	1.25, 1.5, 2.5, 3	1.25/ 2/ 2.5	6.25, 12.5 (scored),@ 15, 25, 50, 100
3 level classification for this paper[17]	**12.5/ 25/ 50**	**1.25/ 2.5/ 5**	**1.25/ 2/ 2.5**	**6.25/ 12.5/ 25**

*Trials using the diuretic as a combination tablet with another anti-hypertensive were excluded.

@Knowledge that the 12.5 mg CTDN tablet is scored is based on a communication from the manufacturer of this tablet to the first author.

Table S2. Gender distribution, mean age, and features of data quality in trials comparing HCTZ with INDAP and HCTZ with CTDN

Author	% men mean age	BP measurement	Blinding	Losses to follow up[3]	Drop outs[3]	Intention -to-treat analysis
Bhigjee (Black patients)	37, 44	Not relevant (study used only for metabolic outcomes)	double	none	none	yes
Bhigjee (Indian patients)	37, 44	Not relevant (study used only for metabolic outcomes)	double	none	none	yes
Elliott[4]	46, 56	Sphygmomanometer, right arm, in triplicate, after 5+ minutes supine.	double	none	none	yes
Emeriau [4]	39, 72	Sphygmomanometer, same arm each visit, triplicate, after 10+ minutes supine.	double	none	none	yes
Kreeft [4]	65, 34-66[3]	Sphygmomanometer, 3 measures averaged, after 15 minutes supine.	double	none	2[1]	yes
Krum	50, 56	Sphygmomanometer, 3 measures averaged, seated	open	none	2[2]	yes
Madkour	43, 55	Supine	open	none	none	yes
Malini	55, 54	Triplicate, after 5+ minutes supine.	open	none	none	yes
Plamte a	37, 52	Supine position.	double	none	none	yes
Plante b	53, 77	Sphygmomanometer, right arm, triplicate with last 2 averaged, after 5+ minutes supine	open	none	none	yes
Radevski	33, 57	Per The American Heart Association.	open	none	None	none
Spence[4]	67, 55	Sphygmomanometer, triplicate, after 10+ minutes supine.	double	none	none	yes
Ernst [4]	53, 48	Taken according to standard guidelines (Pickering 2005) by a study nurse blinded as to diuretic.	Patients only	none	none	Yes
Pareek	37, 44	Not described	Open	none	none	yes
Kwon	46, 50	Oscillometric. 10 minute rest. Supine position	open	none	none	yes

BP: blood pressure

[1]2 of 19 patients were withdrawn for poor adherence.

[2]2 of 20 patients were withdrawn by their personal physicians for "various reasons"

[3]With the exception of Kreeft et al and Krum et al, none of the authors commented explicitly on losses to follow up and drop outs.

[4]Considered a low bias trial.

Table S3. Weight of trial by relative dose level.*

Study	Dosage of HCTZ/INDAP	Relative Dose Levels	Weight In percent
Elliott	25/2.5	Equivalent	3.2
Emeriau	25/1.5 SR	HCTZ level greater	50.0
Kreeft	50/2.5	HCTZ level greater	3.4
Krum	12.5/2.5	INDAP level greater	4.2
Madkour	50/2.5	HCTZ level greater	3.6
Malini	25/2.5	Equivalent	12.0
Plante a	50/2.5	HCTZ level greater	4.0
Plante b	50/2.5	HCTZ level greater	8.0
Radevski	12.5/2.5	INDAP level greater	3.5
Spence	25/2.5	Equivalent	8.1
All Trials			100.0

*Summary results:
Weight from trials with HCTZ level greater than INDAP level = 68.95%
Weight from trials with INDAP level greater than HCTZ level = 7.74%
Weight from trials with HCTZ and INDAP given at the same levels = 23.31%

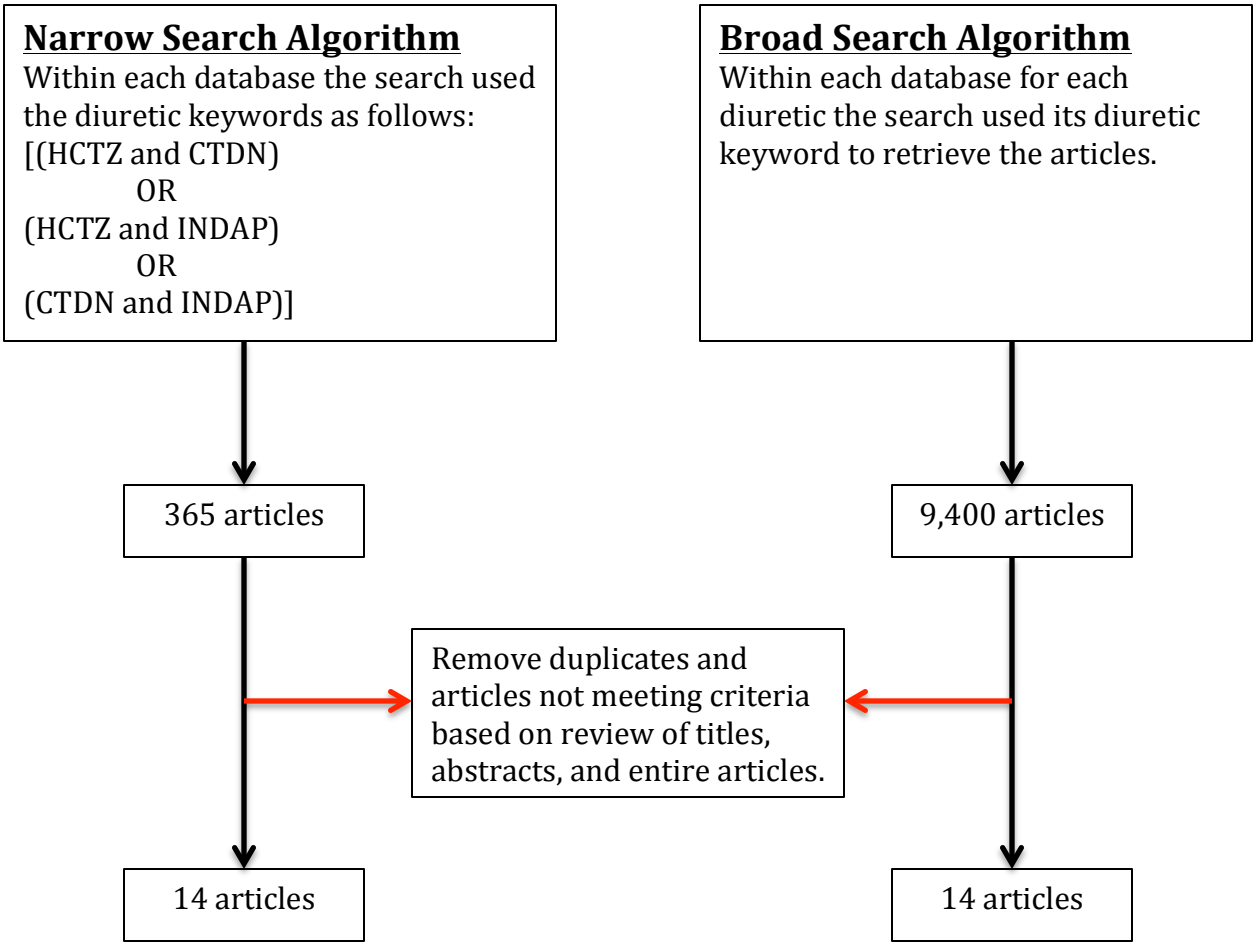


Figure S1. Search algorithms for systematic review. The 3 databases --- PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials --- were searched for randomized trials with systolic BP, metabolic parameters, or cardiovascular events as outcomes and comparing 2 or 3 of the diuretics with one another. For the broad search algorithm, after the keyword for one of the diuretics (e.g., HCTZ) was used to retrieve a set of articles, the search function in Microsoft Word was used to scan titles and abstracts for the other 2 diuretics (e.g., INDAP and CTDN). See text for further inclusion and exclusion criteria. The two search algorithms, narrow and broad, yielded the same 14 articles for review and analysis.

Fig S2a. Effect of removing 1 trial on the systolic blood pressure analysis

Study name	Statistics with study removed			
	Point	Lower limit	Upper limit	p-Value
Elliott	-5.070	-8.110	-2.029	0.001
Emeriau	-6.101	-10.098	-2.103	0.003
Kreeft	-5.001	-7.894	-2.108	0.001
Krum	-5.133	-8.406	-1.860	0.002
Madkour	-4.928	-8.231	-1.625	0.003
Malini	-5.327	-8.860	-1.794	0.003
Plante a	-5.081	-8.396	-1.766	0.003
Plante b	-3.852	-6.428	-1.277	0.003
Radevski	-4.087	-6.612	-1.562	0.002
Spence	-4.110	-6.807	-1.412	0.003
	-4.700	-7.513	-1.886	0.001

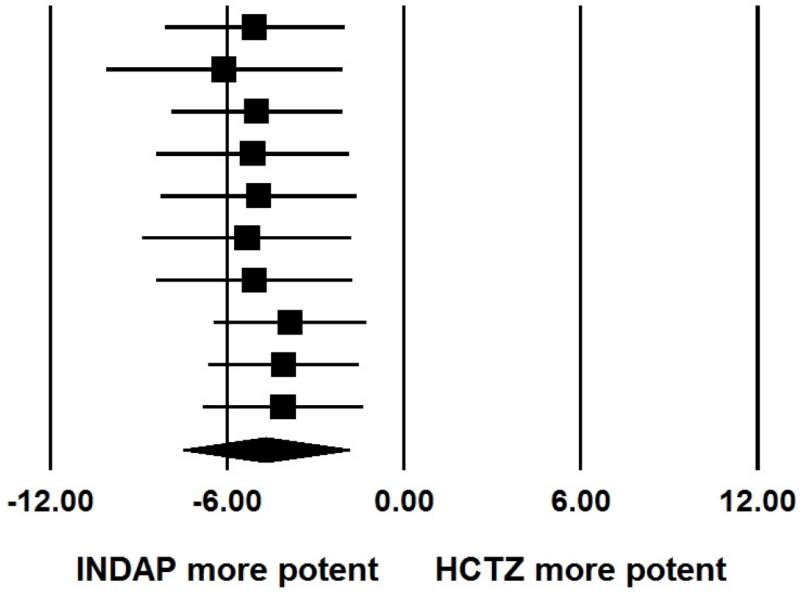


Fig S2b. High and low bias trials in the systolic blood pressure analysis

Group by Bias	Study name	Statistics for each study			
		Difference in means	Lower limit	Upper limit	p-Value
High	Krum	-1.600	-15.146	11.946	0.817
High	Madkour	-6.000	-20.743	8.743	0.425
High	Malini	-3.000	-10.785	4.785	0.450
High	Plante a	-3.000	-16.960	10.960	0.674
High	Plante b	-13.000	-22.705	-3.295	0.009
High	Radevski	-17.000	-31.761	-2.239	0.024
High		-6.786	-11.464	-2.108	0.004
Low	Elliott	2.000	-13.680	17.680	0.803
Low	Emeriau	-3.300	-6.542	-0.058	0.046
Low	Kreeft	3.000	-11.987	17.987	0.695
Low	Spence	-10.050	-19.642	-0.458	0.040
Low		-3.533	-6.768	-0.299	0.032

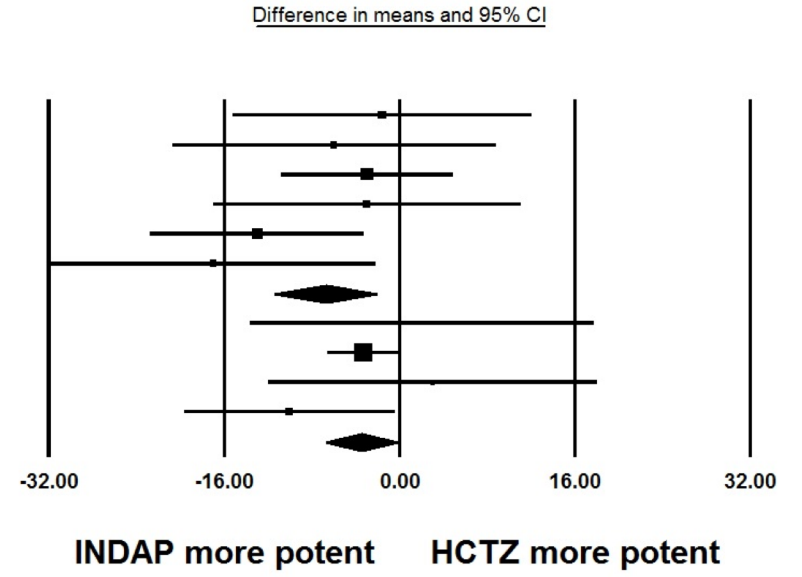


Figure S2a. Removing 1 trial and analyzing the remaining trials for the effect on systolic blood pressure showed that no particular trial accounted for the overall difference between HCTZ and INDAP arms.

Figure S2b. High and low bias trials did not differ significantly in the effect on systolic blood pressure from HCTZ versus INDAP, P = 0.262.

Fig S3a. HCTZ versus INDAP

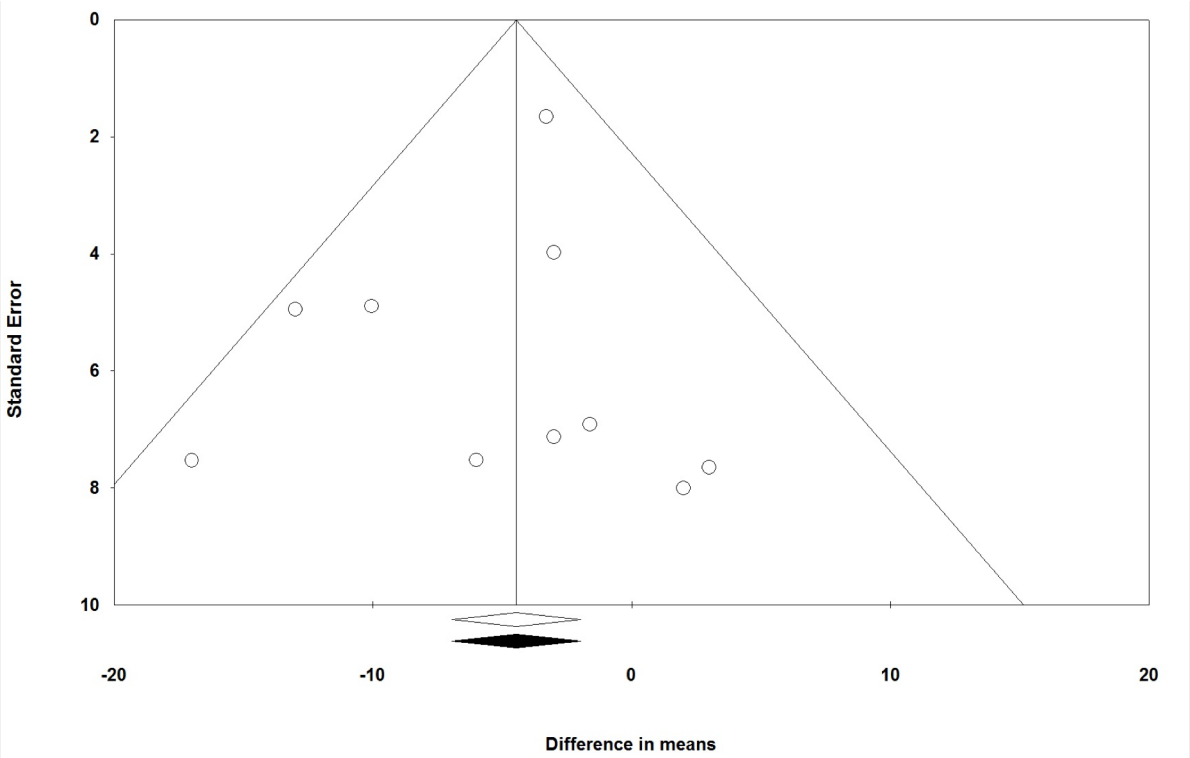
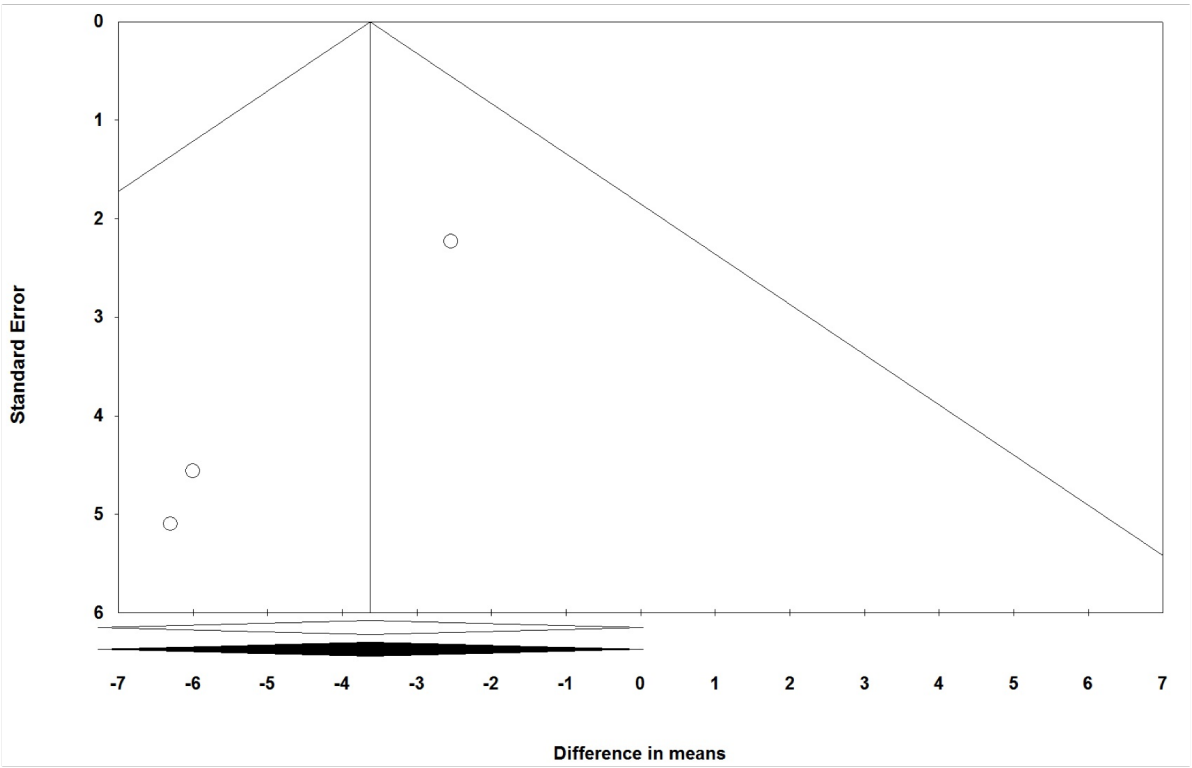


Fig S3b. HCTZ versus CTDN



Figures S3a and S3b. Funnel plots for mean systolic blood pressure reduction by INDAP and CTDN compared to HCTZ for observed differences (clear diamonds) and differences adjusted for small studies (solid diamonds). There was no evidence for publication bias for either analysis.

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CLINICAL RESEARCH

Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin–angiotensin–aldosterone system inhibitors involving 158 998 patients

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Aims Renin–angiotensin–aldosterone system (RAAS) inhibitors are well established for the reduction in cardiovascular morbidity, but their impact on all-cause mortality in hypertensive patients is uncertain. Our objective was to analyse the effects of RAAS inhibitors as a class of drugs, as well as of angiotensin-converting enzyme (ACE) inhibitors and AT1 receptor blockers (ARBs) separately, on all-cause mortality.

Methods and results We performed a pooled analysis of 20 cardiovascular morbidity–mortality trials. In each trial at least two-thirds of the patients had to be diagnosed with hypertension, according to the trial-specific definition, and randomized to treatment with an RAAS inhibitor or control treatment. The cohort included 158 998 patients (71 401 RAAS inhibitor; 87 597 control). The incidence of all-cause death was 20.9 and 23.3 per 1000 patient-years in patients randomized to RAAS inhibition and controls, respectively. Overall, RAAS inhibition was associated with a 5% reduction in all-cause mortality (HR: 0.95, 95% CI: 0.91–1.00, $P = 0.032$), and a 7% reduction in cardiovascular mortality (HR: 0.93, 95% CI: 0.88–0.99, $P = 0.018$). The observed treatment effect resulted entirely from the class of ACE inhibitors, which were associated with a significant 10% reduction in all-cause mortality (HR: 0.90, 95% CI: 0.84–0.97, $P = 0.004$), whereas no mortality reduction could be demonstrated with ARB treatment (HR: 0.99, 95% CI: 0.94–1.04, $P = 0.683$). This difference in treatment effect between ACE inhibitors and ARBs on all-cause mortality was statistically significant (*P*-value for heterogeneity 0.036).

Conclusion In patients with hypertension, treatment with an ACE inhibitor results in a significant further reduction in all-cause mortality. Because of the high prevalence of hypertension, the widespread use of ACE inhibitors may result in an important gain in lives saved.

Keywords Hypertension • ACE inhibitor • ARB • Meta-analysis • Mortality

Introduction

The World Health Organization describes hypertension as the number one risk factor for mortality, as worldwide annually 7.5 million deaths (13% of all deaths) are attributable to high blood pressure (BP)-related diseases, particularly cardiovascular diseases (CVD).[1] For that reason, the guidelines of hypertension and cardiology societies emphasize that hypertension treatment should aim

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at reducing the long-term risk of (cardiovascular) morbidity and mortality.[2,3] Hypertension is often referred to as the 'silent killer', as its presence is usually symptomless. Therefore, compliance to antihypertensive medication is a challenge for most patients, especially as adequate BP control often requires the use of multiple agents, causing additional side effects and as a result inferior adherence.[2] Thus, there is a continuing need for potent medications, preferably with beneficial effects on mortality, to improve patients' adherence to the treatment prescribed.

The benefits of antihypertensive treatment on cardiovascular morbidity are thought to be mainly due to the BP-lowering effect *per se*, independent of the class of drug employed, as has been demonstrated with β-blockers, diuretics, calcium channel blockers, and recently with the renin–angiotensin–aldosterone system (RAAS) inhibitors.[2] Blockade of the RAAS is one of the key therapeutic targets in patients with hypertension, as an overactive RAAS is strongly associated with high BP. The RAAS controls circulating volume and electrolyte balance in the human body and is therefore an important regulator of haemodynamic stability.[4] RAAS inhibitors are the most widely prescribed class of drugs for the management of hypertension. Currently, the most clinically relevant pharmacological agents that block the RAAS are angiotensin-converting enzyme (ACE) inhibitors and AT1 receptor blockers (ARBs). Both drugs block angiotensin II, but ACE inhibitors are characterized by a decrease in the degradation of bradykinin leading to a release of nitric oxide and prostaglandins resulting in additional vasodilatation. These differences in modes of action between ACE inhibitors and ARBs might have clinical implications for patients with hypertension.[5]

Reductions in both cardiovascular morbidity and mortality have been well demonstrated with RAAS inhibitors across specific populations that were selected and included for a criterion other than hypertension *per se*. For example, SOLVD (enalapril in heart failure), HOPE (ramipril in patients with high CVD risk), and EUROPA (perindopril in stable coronary disease) demonstrated significant reductions in the composite endpoint of death from cardiovascular causes, myocardial infarction or stroke with ACE inhibitors. In these trials, less than half of the patients enrolled had prevalent hypertension.[6–8] The beneficial effects of RAAS inhibitors on (all-cause) mortality (a guideline-recommended goal of antihypertensive therapy)[2] have not been convincingly demonstrated in the indication of hypertension. Furthermore, most (antihypertensive) trials in which the clinical effects of RAAS inhibitors were evaluated were underpowered for this endpoint.[9–11] To evaluate the impact of RAAS inhibitors on all-cause and cardiovascular mortality for their main indication, hypertension, we undertook a meta-analysis of all prospective randomized clinical trials that compared RAAS inhibitors with control therapy in different populations in which the absolute majority of the patients had hypertension, and where the expected benefits would mainly come from a decrease in BP.

We hypothesized that, taken all evidence together, RAAS inhibitors would produce a significant mortality reduction compared with (contemporary) control therapy. Although the primary aim of this meta-analysis decided *a priori* was to evaluate RAAS inhibitors as a class of drugs, we realized that ACE inhibitors and ARBs have partly different modes of action. Therefore, we decided to also study these two classes of drugs separately.

We argued that, if a significant effect on both all-cause and cardiovascular mortality could be demonstrated, then treating physicians would have an additional argument to motivate hypertensive patients to comply with long-term treatment with these agents.

Methods

Study selection

We intended to include all publicly available morbidity–mortality prospective randomized controlled trials that compared active treatment with an ACE inhibitor or an ARB with control treatment (placebo, active control, or usual care).

Trials were identified by a systematic search of OVID MEDLINE and (ADIS) ISI Web of Science using a broad range of key words, including 'antihypertensive agents', 'angiotensin-converting enzyme inhibitors', 'angiotensin II Type 1 receptor blockers', 'hypertension', and 'mortality', published in English between 1 January 2000 and 1 March 2011. We decided to start our search in the year 2000, because of our intention to evaluate the effect of RAAS inhibition on top of contemporary treatment and considered the HOPE trial to be a landmark study in this respect (published in the year 2000).[7] References of identified papers and abstract listings of annual meetings of the American Heart Association, the American College of Cardiology, European Society of Cardiology, the American Society of Hypertension, the European Society of Hypertension, and the Council for High Blood Pressure Research were also examined during the same period. Each trial identified in this search was critically and independently evaluated by two investigators (L.v.V. and K.M.A.) for patient population, study treatment, protocol, and endpoints.

A total of 512 publications met the above-mentioned search criteria (*Figure 1*). We selected trials including different hypertensive populations for whom the benefits of RAAS inhibition would be expected to be mainly due to BP reduction. We only included the principal study publication, and excluded *post hoc* and subgroup analyses. Furthermore, we excluded trials in which patients were selected because of a specific disease, such as heart failure, acute coronary syndromes, acute stroke, haemodialysis, atrial fibrillation, or post-cardiac surgery patients, because of the expected benefits of RAAS inhibition beyond BP lowering in these patient populations.[12,13]

Forty-four randomized controlled trials using RAAS blockade were identified that corresponded with the inclusion criteria. We additionally excluded eight trials in which less than two-thirds (66.7%) of the studied population were diagnosed with hypertension, according to the trial-specific definition. Ten trials were excluded due to either a low number of participants ($n < 100$) or a low incidence of all-cause death ($n < 10$), the primary endpoint of this study. Moreover, one trial was excluded because all-cause mortality was not reported. Finally, five trials (including INVEST, ACCOMPLISH, and ONTARGET) were excluded because RAAS inhibitors were used simultaneously in both trial arms.[14–16] Thus, a total of 20 trials were included in our analysis (*Figure 1*), which had a follow-up duration of at least 1 year.

Data extraction

This analysis is based on data that were obtained from the papers reporting trials' main results. Two authors (L.v.V., K.M.A.) independently extracted data from these reports, and resolved differences by consensus. For each treatment arm, we recorded the number of trial participants, the number of patients who reached the endpoint of all-cause and cardiovascular mortality, the mean age at baseline,

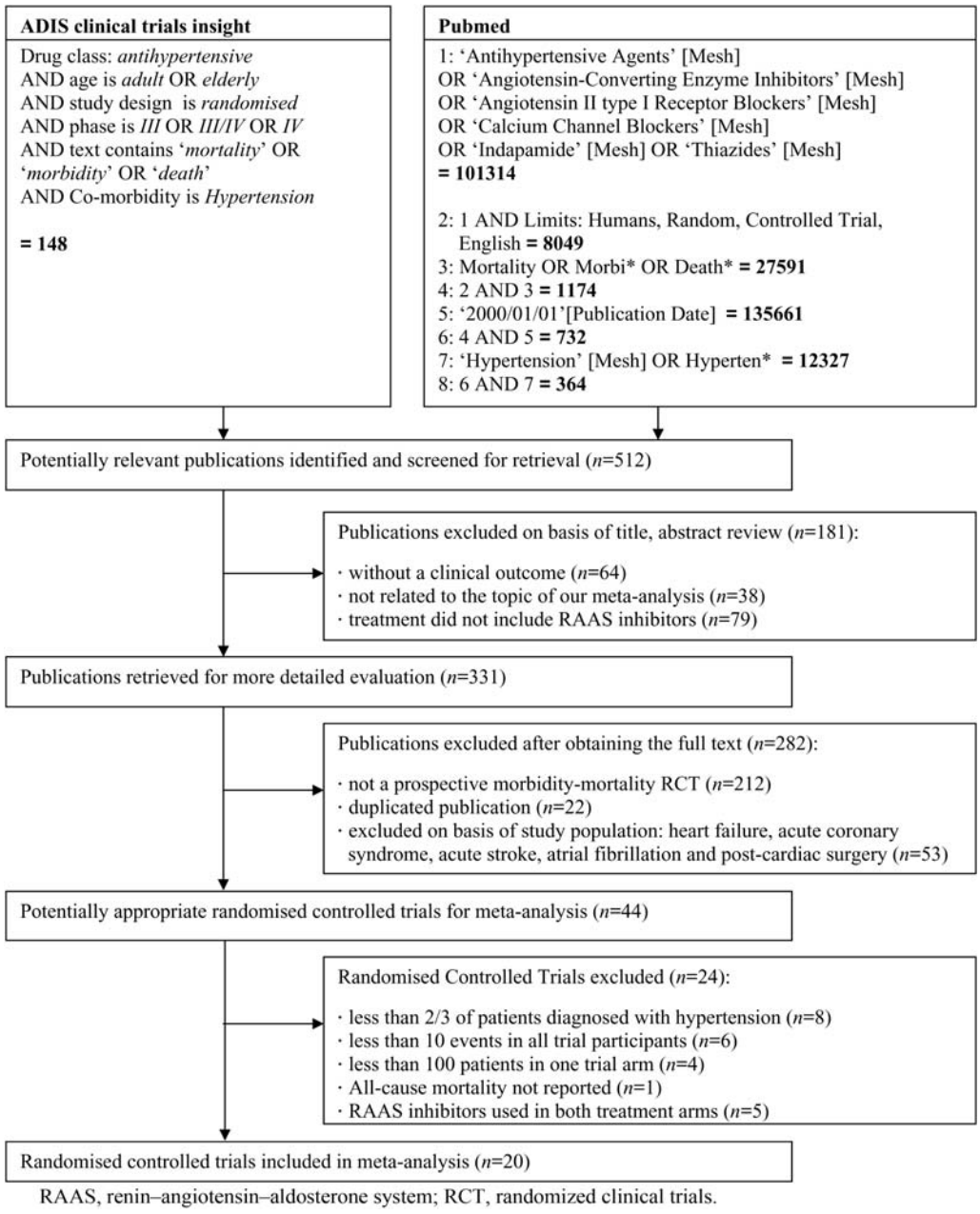

Figure 1 Flow diagram of trial search and selection process. RAAS, renin–angiotensin–aldosterone system; RCT, randomized clinical trials.

the mean diastolic blood pressure and systolic blood pressure (SBP) at baseline, the percentage of male participants, the percentage of patients with diabetes mellitus, renal insufficiency, and hypertension, as well as the total follow-up time (until death) in years.

Endpoint definition

The endpoints of this pooled analysis were all-cause and cardiovascular mortality during long-term follow-up. Data on all-cause death were available for all trials. Data on cardiovascular death were not available for RENAAL, IDNT, MOSES, and CASE-J.

We aimed to provide estimates of the incidence of these endpoints in patients randomized to RAAS inhibitors and control therapy, as well as estimates of the absolute and relative reduction in the incidence of the endpoints by RAAS inhibitors. Since the duration of follow-up varied between the trials, we decided to base our analyses on the mortality incidence rate (IR), which was assumed to be constant over time in each of the comparison groups. The IR is defined as the number of patients who reached the endpoint in the comparison group divided by the patient-years of follow-up in the corresponding group (i.e. the sum of the follow-up times for each individual). The latter figure is equal to the number of patients multiplied by their mean follow-up duration.

To obtain the trial- and treatment-arm specific mean follow-up duration, the following five-step approach was applied. Firstly, we observed whether the mean follow-up time per treatment arm was

stated in the paper. If this was not available, we then derived it from the reported death rate by dividing the total number of deaths by the annual death rate. If these data were not available, then the mean follow-up time was estimated from incidences that were derived from Kaplan–Meier curves, in combination with the number of patients that were reported to be at risk at several follow-up points. Finally, if we were not able to compute the mean follow-up duration for each treatment arm separately, we used the mean follow-up time that was reported for all trial participants together.

Statistical analysis

For each individual trial, the treatment-arm specific all-cause and cardiovascular mortality IR was determined. We evaluated the assumption that the mortality rate is constant over time by visually inspecting the Kaplan–Meier curves of the studies in this meta-analysis, comparing different time windows within each Kaplan–Meier curve. We did not find any major deviation from this assumption. Furthermore, we realized that the follow-up time within each of the trials is relatively short (the overall mean follow-up duration is 4.3 years). Thus, on average, during the course of the trial, patients became only 4 years older. In view of this fact, it seems reasonable to assume that the IRs were constant over time.

Information on follow-up times is needed to obtain estimates of absolute risks (and absolute treatment effects). However, because of the assumptions that we used, our IR estimates might be somewhat inaccurate. Therefore, we based our estimates of relative treatment effects on the hazard ratios (HRs) and confidence intervals (CIs) or standard errors that were reported for each trial. Actually, HRs were available for all trials, except for RENAAL, SCOPE, and pilot HYVET. For these trials, we calculated HRs based on the IRs in the separate treatment arms.

Because of the large variety in active (and control) treatments, we used a random-effects model to compute an overall pooled HR, even in case statistical tests for heterogeneity across trials were non-significant. Statistical heterogeneity was tested by Cochran's Q statistic,[17] and a P-value <0.10 (two sided) was considered to indicate heterogeneity among trials. The degree of heterogeneity was presented as an I^2 value. Publication bias was assessed by visually examining funnel plot asymmetry and quantified by using an Egger regression test to calculate two-tailed P-values.[18]

We hypothesized that the mortality reduction by antihypertensive drugs might be influenced by age, gender, baseline SBP, BP reduction during follow-up, and follow-up time. To evaluate this hypothesis, we conducted linear regression analyses, based on trial-level data (so-called 'meta-regression'). The trial-specific mean age, percentage of men, mean SBP, mean difference in BP reduction after 1 year of follow-up between RAAS inhibitors and control therapy, and mean follow-up time were considered as explanatory variables of the natural logarithm of the trial-specific hazard ratio (lnHR) for all-cause mortality. In this analysis, trial-level observations were weighed according to the inverse of the squared standard error of lnHR, thus taking into account the amount of 'statistical information' that is produced by each trial. Secondly, by including follow-up time in this analysis we were able to assess whether the mortality incidence ratio is constant over time.

Although we hypothesized that, taken all evidence together, RAAS inhibitors as a class of drugs would produce a homogenous treatment effect in terms of a mortality reduction compared with (contemporary) control therapy, we also performed stratified analyses according to the class of drug (ACE inhibitor vs. ARBs), as we realized that ACE inhibitors and ARBs have partly different modes of action. We also performed stratified analyses according to type of control (placebo vs. active treatment), and percentage of patients with diabetes mellitus or renal insufficiency at baseline (>50% vs. <50%). Pooled HRs for all-cause mortality were determined using a random effects model for each stratum, and differences between strata were studied.

All statistical tests were two-sided, and a P-value <0.05 was considered significant. We used SAS 9.2 for Windows for data analysis.

Results

Trial characteristics

A total of 20 trials fulfilled all selection criteria for this meta-analysis, and their main characteristics are presented in *Table 1*.[9–11,19–35] In total 158 998 patients were randomized to RAAS inhibitor therapy ($n = 71\,401$; 299 982 patient-years of follow-up) or control treatment ($n = 87\,597$; 377 023 patient-years of follow-up). ACE inhibitors were used as the active treatment in seven trials ($n = 76\,615$); two of these studies were placebo controlled.[23,24,26,30,31,33,34] Thirteen trials, of which five were placebo-controlled, allocated participants to an ARB as the active treatment ($n = 82\,383$).[9–11,19–22,25,27–29,32,35]

Patient characteristics

On average, 91% of the trial participants were hypertensive according to the definition used in each trial. The mean baseline SBP was 153 mmHg (range of the means across trials 135–182), the mean age was 67 years (range of the means across trials 59–84) and 58% of participants were man (range of this percentage across trials 36–80; *Table 1*).

All-cause mortality

During a mean follow-up of 4.3 years, 6284 of the patients assigned to an RAAS inhibitor reached the endpoint of all-cause death. This corresponds with an IR of 20.9 deaths per 1000 patient-years. During the same period, a total of 8777 patients assigned to control therapy had all-cause death, implying an IR of 23.3 deaths per 1000 patient-years. RAAS inhibition was associated with a statistically significant reduction in all-cause mortality in three individual trials, ASCOT-BPLA, ADVANCE, and HYVET (*Figure 2*).[23,26,31]

In all 20 trials grouped together, treatment with an RAAS inhibition was associated with a statistically significant 5% reduction in all-cause mortality (HR: 0.95, 95% CI: 0.91–1.00, $P = 0.032$; *Figure 2*). The degree of heterogeneity in the treatment effect across all trials was low (I^2: 15%) and non-significant ($P = 0.266$). No funnel-plot asymmetry was visualized, and the P-value using an Egger regression test for all-cause mortality was >0.10 (intercept −0.3, 95% CI: −1.3–0.68; $P = 0.53$), indicating no evidence for publication bias.

Cardiovascular mortality

Excluding the four trials that did not report on cardiovascular mortality, 2570 patients assigned to RAAS inhibition had cardiovascular death. Based on a total of 295 617 patient-years of follow-up, the IR was 8.7 per 1000 patient-years. The IR in patients assigned to control therapy was 10.1 per 1000 patient-years (3773 events;

Table 1 Baseline characteristics of study population in 20 trials (n = 158 998

Trial acronym	Year	n	Active drug	Control	Mean follow-up, years	Hypertension, %	Mean SBP, mmHg	Mean age (years)	Men, %	IR in control group
RENAAL[9]	2001	1513	Losartan	Placebo	3.09	96.5	153	60.0	63.2	66.0
IDNT[28]	2001	1715	Irbesartan	Amlodipine or placebo	2.86	100	159	58.9	66.5	54.0
LIFE[25]	2002	9193	Losartan with and without HCTZ	Atenolol with and without HCTZ	4.82	100	174	66.9	46.0	19.5
ALLHAT[30]	2002	33 357	Lisinopril	Chlorthalidone or amlodipine	5.01	100	146	66.9	53.3	28.5
ANBP-2[33]	2003	6083	ACE inhibitor (enalapril)	Diuretic (HCTZ)	4.06	100	168	71.9	49.0	17.1
SCOPE[29]	2003	4937	Candesartan	Placebo	3.74	100	166	76.4	35.5	29.0
pilot HYVET[24]	2003	1283	Lisinopril	Diuretic or no treatment	1.12	100	182	83.8	36.6	55.4
JMIC-B[34]	2004	1650	ACE inhibitor	Nifedipine	2.25	100	146	64.5	68.8	6.2
VALUE[27]	2004	15 245	Valsartan	Amlodipine	4.32	100	155	67.3	57.6	24.8
MOSES[32]	2005	1352	Eprosartan	Nitrendipine	2.50	100	152	68.1	54.2	31.0
ASCOT-BPLA[26]	2005	19 257	Amlodipine with and without perindopril	Atenolol with and without bendroflumethiazide	5.50	100	164	63.0	76.6	15.5
JIKEI HEART[11]	2007	3081	Valsartan	Non-ARB	2.81	87.6	139	65.0	66.3	6.2
ADVANCE[31]	2007	11 140	Perindopril with indapamide	Placebo	4.30	68.7	145	66.0	57.5	19.8
HYVET[23]	2008	3845	Indapamide with and without perindopril	Placebo	2.11	89.9	173	83.6	39.5	59.3
PRoFESS[22]	2008	20 332	Telmisartan	Placebo	2.50	74.0	144	66.2	64.0	29.1
TRANSCEND[35]	2008	5926	Telmisartan	Placebo	4.67	76.4	141	66.9	57.0	25.2
CASE-J[20]	2008	4703	Candesartan	Amlodipine	3.30	100	163	63.8	55.2	11.1
HIJ-CREATE[19]	2009	2049	Candesartan	Non-ARB	4.03	100	135	64.8	80.2	14.3
KYOTO HEART[21]	2009	3031	Valsartan	Non-ARB	2.92	100	157	66.0	57.0	7.2
NAVIGATOR[10]	2010	9306	Valsartan	Placebo	6.10	77.5	140	63.8	49.4	11.5

HCTZ, hydrochlorothiazide; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; SBP, systolic blood pressure; IR, incidence rate per 1000 patient-years.

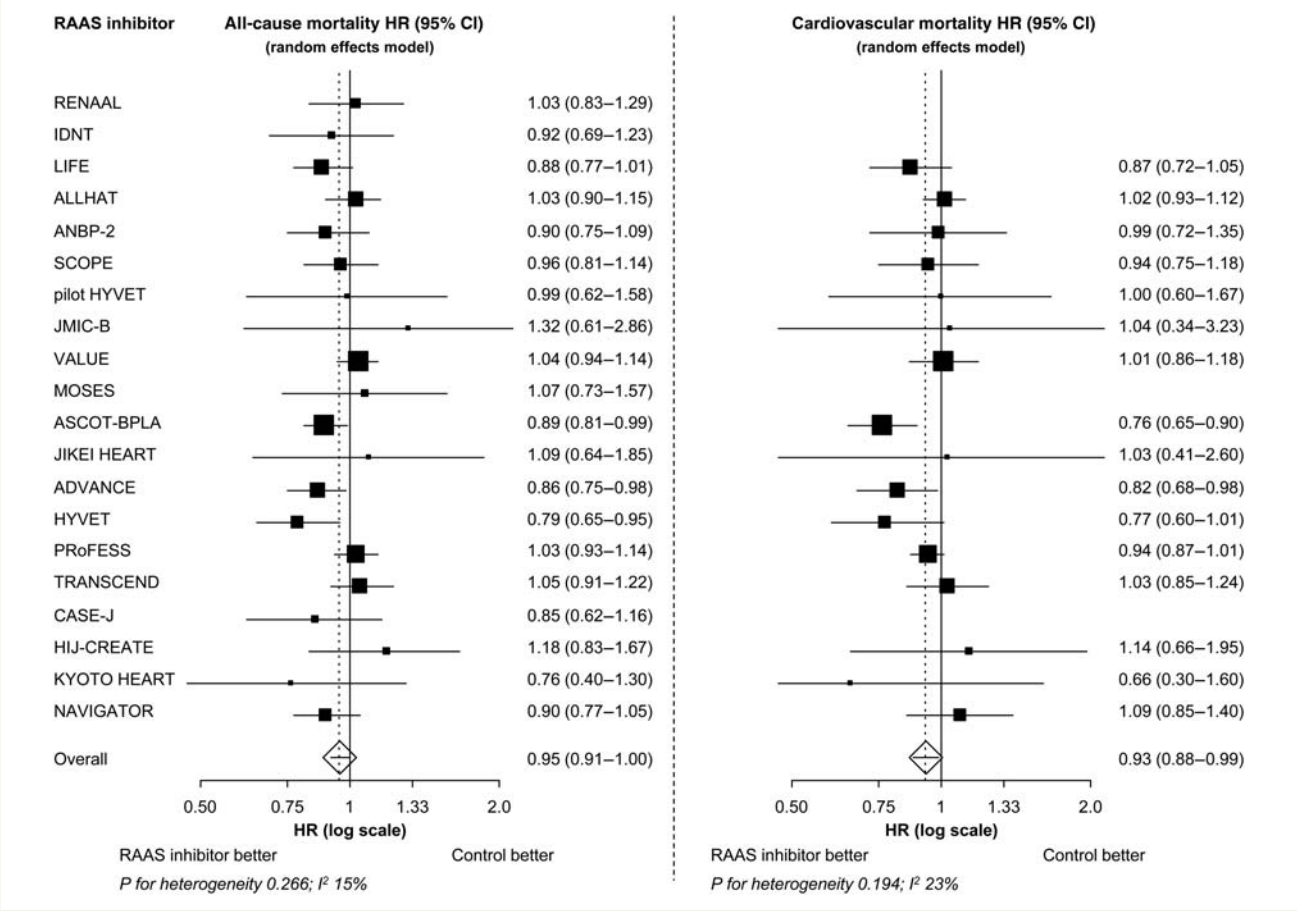

Figure 2 All-cause and cardiovascular mortality treatment effect of renin–angiotensin–aldosterone system blockade in all included trials. HR, hazard ratio; CI, confidence interval; RAAS, renin–angiotensin–aldosterone system. Overall $P = 0.032$ for all-cause mortality. Overall $P = 0.018$ for cardiovascular mortality.

372 105 patient-years of follow-up), resulting in a significant 7% overall reduction in cardiovascular mortality (HR: 0.93, 95% CI: 0.88–0.99, $P = 0.018$; *Figure 2*). The degree of heterogeneity in treatment effect across all trials was low (I^2: 23%) and non-significant ($P = 0.194$). There was no evidence of publication bias.

Angiotensin-converting enzyme inhibitors vs. AT1 receptor blockers

All seven trials together, ACE inhibitors were associated with a statistically significant 10% reduction in all-cause mortality (IR: 20.4 vs. 24.2 deaths per 1000 patient-years; HR: 0.90, 95% CI: 0.84–0.97, $P = 0.004$). No significant mortality reduction could be demonstrated with ARB treatment (13 trials; IR: 21.4 vs. 22.0 deaths per 1000 patient-years; HR: 0.99, 95% CI: 0.94–1.04, $P = 0.683$). This difference in the treatment effect between ACE inhibitors and ARBs was statistically significant (*P*-value for interaction 0.036). Apparently, the observed mortality reduction in the overall group of RAAS inhibitors was completely driven by the beneficial effect of the ACE inhibitors.

As far as the ACE inhibitor trials are concerned, the largest mortality reductions were observed in ASCOT-BPLA, ADVANCE, and HYVET, all of which studied the ACE inhibitor perindopril (pooled HR: 0.87, 95% CI: 0.81–0.93, *P*-value <0.001). However, there was no evidence of heterogeneity among the ACE inhibitor trials in the effect of the studied ACE inhibitor regimen on all-cause mortality (*P*-value for heterogeneity 0.310, I^2: 16%; *Figure 3*). There was also no evidence of heterogeneity in the effect of ARBs (*P*-value for heterogeneity 0.631, I^2: 0%).

Patients randomized to an ACE inhibitor had 9.1 *cardiovascular* deaths per 1000 patient-years, compared with 11.2 in their controls (HR: 0.88; 95% CI: 0.77–1.00; $P = 0.051$). In the ARB trials, the IRs were 8.8 and 9.2 cardiovascular deaths per 1000 patient-years for patients assigned to ARB and control therapy, respectively (HR: 0.96; 95% CI: 0.90–1.01; $P = 0.143$). The test for heterogeneity in effects on *cardiovascular* mortality between ACE inhibitors and ARBs was statistically non-significant ($P = 0.227$).

Meta-regression

Multiple linear regression analysis showed a significant ($P = 0.035$) association between the trial-specific mean SBP (measured at baseline), and the relative mortality reduction by RAAS blockade. The mortality reduction was largest in trials with the highest mean

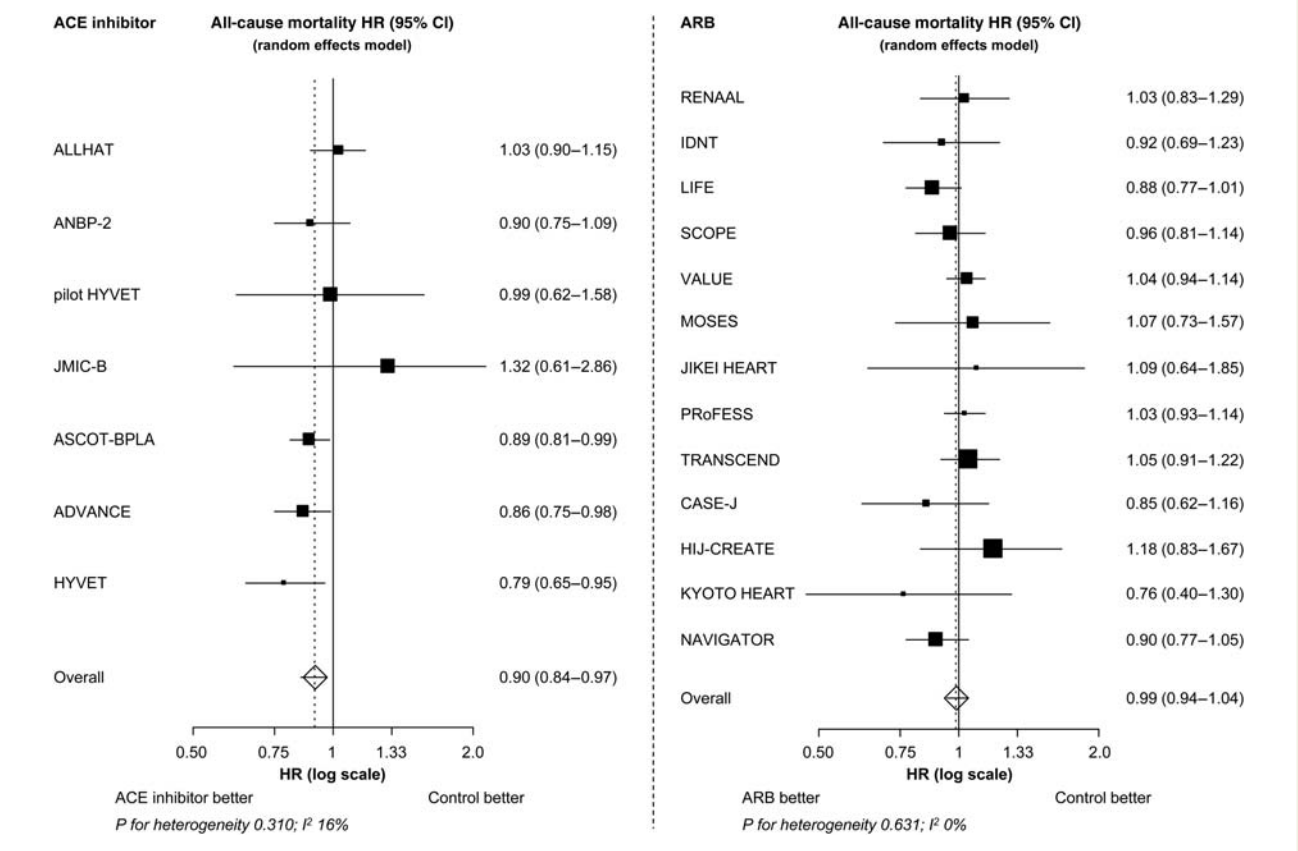

Figure 3 The all-cause mortality treatment effect of ACE inhibitor and ARB trials. HR, hazard ratio; CI, confidence interval; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker. $P = 0.004$ for the treatment effect of ACE inhibitor on all-cause mortality. $P = 0.683$ for the treatment effect of ARB on all-cause mortality.

baseline BP values. Secondly, there was a significant ($P = 0.008$) relation between the trial specific mean difference in BP between the studied RAAS inhibitor and control therapy at 1-year follow-up, and the mortality reduction produced by the RAAS inhibitor. The mortality reduction was largest in trials with the largest difference in mean SBP reduction. No significant association was found between the trial-specific mean age, man/woman ratio, mean follow-up time and the mortality reduction by RAAS blockade. Mean follow-up time was also not related to the observed mortality reduction, supporting our hypothesis that the mortality incidence ratio is constant over time (at least for the mean duration of 4.3 years).

Stratified analyses

Similar HRs for all-cause mortality were found in clinical trials that compared RAAS inhibition with placebo (HR: 0.95, 95% CI: 0.88–1.02, $P = 0.177$) and with active control (HR: 0.95, 95% CI: 0.91–1.01, $P = 0.066$; P-value for interaction 0.889). Likewise, no heterogeneity in treatment effect was observed with respect to the percentage of participants with diabetes mellitus or renal insufficiency.

Discussion

This meta-analysis, which included almost 160 000 patients, sought to evaluate the effect of RAAS inhibitors as a class of drugs on total and cardiovascular mortality in their main indication hypertension. Overall, the results show a 5% reduction in all-cause mortality during a 4-year follow-up period associated with the class of RAAS inhibitors. This mortality reduction was found when compared with placebo, as well as in comparison with other BP-lowering drugs. However, in a stratified analysis according to the class of drug, it was shown that the observed overall all-cause mortality reduction was almost completely a result of the beneficial effect of the class of ACE inhibitors (10% relative reduction in all-cause mortality), whereas the ARBs showed a neutral treatment effect. The findings are firm, as the analysis included a large number of patient-years (677 005) and endpoints (15 061 deaths). The findings are relevant to clinical practice, as they are based on data from well-designed randomized trials encompassing a broad population of patients with high BP, who were well-treated for concomitant risk factors and who represent usual hypertensive patients seen today.

Reduction in mortality is the primary goal of antihypertensive therapy.[2] Paradoxically, the effect of RAAS inhibitors on mortality

in hypertensive patients remained uncertain and had never been systematically evaluated. To our knowledge, no prior published meta-analysis investigated the efficacy of RAAS inhibitors on all-cause and cardiovascular mortality in their main indication of hypertension. Previous analyses in for example heart failure or coronary artery disease populations (with or without hypertension) demonstrated a reduction in cardiovascular events, stroke, and mortality.[36,37] In addition, a pooled analysis of trials in patients with cardiovascular disease (including hypertension) concluded that the reduction in cardiovascular mortality and stroke with RAAS inhibitors is BP dependent.[38] In our analyses, the significant reduction in cardiovascular mortality associated with RAAS inhibition supports previous literature.

As stated, the primary aim of this meta-analysis decided *a priori* was to test the hypothesis that RAAS inhibitors as a class of drugs would have a beneficial effect on total mortality in hypertension, when compared with contemporary control antihypertensive therapy. However, as we realized that, among the RAAS inhibitors, the ACE inhibitors and ARBs have different mechanisms of action, we also decided to study whether there was a differential effect on mortality between these two classes of drugs. Indeed, our analysis clearly showed that nearly all of the mortality reduction was observed with ACE inhibitors. Contrary, there was no clear benefit from the ARBs. This was supported by the sensitivity analysis which showed a significant stronger treatment effect in the ACE inhibitor trials compared with the ARB trials. With respect to this finding several points deserve consideration.

The reduced effect of ARBs on mortality when compared with ACE inhibitors has also previously been discussed.[39,40] A recent meta-analysis of 37 ARB trials also failed to detect a reduction in all-cause or cardiovascular mortality in a broad population of patients.[41] The differences in the modes of action between ACE inhibitors and ARBs, and the small-but-definite BP-independent reduction in CAD mortality with ACE inhibitors, which has not been observed with ARBs or other antihypertensive agents, might contribute to this finding.[42] On the other hand, others have demonstrated that BP-dependent beneficial effects in the prevention of stroke and heart failure are similar for ACE inhibitors and ARBs. ACE inhibitors and ARBs have also been shown to be equally effective in preventing atrial fibrillation and new-onset diabetes.[43,44] Furthermore, it should be emphasized that we did not design this meta-analysis to make a head-to-head comparison between ACE inhibitors and ARBs. The finding that the beneficial effect is seen in the ACE inhibitor population as opposed to the ARB population should be considered a *post hoc* observation. Given the nature of meta-analyses, which are per definition data-driven, the differential effect between ACE inhibitors and ARBs should be interpreted with caution to avoid overstating this subgroup finding vis-à-vis the *a priori* hypothesis. In this respect it should also be noted that the difference in effect on *cardiovascular* mortality between ACE inhibitors and ARBs was not statistically significant. Furthermore, two previous studies were designed to compare ACE inhibitors and ARBs in an hypertensive population, but both the ONTARGET (telmisartan vs. ramipril) and DETAIL (telmisartan vs. enalapril) trial did not show a differential treatment effect between ARBs and ACE inhibitors.[15,45] Thus, at present, the results of this analysis do not warrant changing clinical practice treatment guidelines that recommend that an ARB may be used in ACE inhibitor-intolerant hypertensive patients.[2] Hopefully, our findings will form the basis of further analysis and studies into the effects of BP treatment and total mortality which is the first line priority in the guidelines for the management of hypertension.

It might be argued that the observed 5% relative mortality reduction in the overall group of RAAS inhibitors, and the 10% relative mortality reduction in the ACE inhibitor group is small, and only found to be statistically significant in our analysis because of statistical 'overpowering'. Indeed, in meta-analyses clinically irrelevant treatment effects might become statistically significant (i.e. the estimated effect divided by the standard error is >1.96) simply because of the large size of the aggregate (or pooled) trials. In our view, however, the observed mortality reduction in this meta-analysis is clinically relevant indeed, for several reasons. Firstly, it should be realized that the treatment effect was reached in patients who did receive a broad range of other contemporary risk-reduction therapies, including statins, antiplatelet therapy, beta-blockers, diuretics, and other BP-lowering medication (note that, as per design, we included trials that were conducted during 2000–2011). Secondly, the estimated absolute mortality reduction was 2.4 per 1000 patient-years for the RAAS inhibitors as a group and 3.8 per 1000 patient-years for the class of ACE inhibitors. This is an interesting figure, particularly since the prevalence of hypertension in Western (CAD) populations is high,[46] despite the widespread use of BP-lowering medication. Thus a wider application of these agents, in particular of ACE inhibitors, may have substantial effects on the population level. Interestingly, the observed mortality reduction was largest in trials with the highest baseline SBP. The observed mortality reduction may be used as an additional argument to stimulate patients to adhere to the prescribed treatment.

Limitations

Several limitations of our analysis have to be mentioned. Firstly, there was a great deal of variation between the studied populations. For example, trials used different definitions of hypertension, different dosages of the active and control drug, different target BP levels, different follow-up times, and in several studies patients had other concomitant conditions and background therapy. Although this does not hamper the generalizability of our results, it makes it challenging to accurately estimate the effect of RAAS inhibition in a broad range of routine clinical practice situations.

Secondly, this meta-analysis is based on trial level data, rather than on individual patient data. Information on background therapy and co-morbidities were not available in several trial reports. Thus, we could not reliably analyse the relation between these factors and the observed mortality reduction. Moreover, the treatment arm-specific follow-up time was not available in all trials, we therefore derived follow-up time from either the reported death rate, Kaplan–Meier curves, or mean follow-up duration. This is an approximation of the true follow-up time, and we appreciate that our estimates of mortality incidence might be somewhat over or underestimated. However, importantly, this methodology had not influenced the estimation of the observed relative mortality reduction, which was mainly based on the HRs that were reported for the separate trials.

Finally, this meta-analysis assumed a class effect among the different ACE inhibitors and ARBs. The validity of this concept was not challenged by formal statistical tests on heterogeneity of treatment effects among the different (ACE inhibitor and ARB) trials. Still, it should be realized that differences may exist between drugs within the same class that are simply missed due to lack of statistical power. It should therefore be emphasized that our findings should be interpreted in relation to the pharmacological properties of the applied agents.

Conclusion

This meta-analysis, which involved almost 160 000 patients, demonstrated that RAAS inhibitors as a class of antihypertensive drugs were associated with a significant 5% relative reduction in all-cause mortality in populations with a high prevalence of hypertension when compared with contemporary control antihypertensive therapy. Stratified subgroup analysis according to class of drug showed a differential treatment effect between ACE inhibitors and ARBs. The overall reduction in all-cause mortality resulted almost completely from the class of ACE inhibitors, which were associated with a statistically significant 10% relative reduction in all-cause mortality, whereas no mortality reduction was observed with the ARBs. In view of the high prevalence of hypertension in the general population, widespread use of ACE inhibitors may therefore result in a considerable gain in lives saved. The results of this study provide a convincing argument to improve treatment adherence in the millions of people around the world suffering from hypertension and its sequelae.

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Original Investigation

Effect of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on All-Cause Mortality, Cardiovascular Deaths, and Cardiovascular Events in Patients With Diabetes Mellitus

A Meta-analysis

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IMPORTANCE Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) may have different effects on cardiovascular (CV) events in patients with diabetes mellitus (DM).

OBJECTIVE To conduct a meta-analysis to separately evaluate the effects of ACEIs and ARBs on all-cause mortality, CV deaths, and major CV events in patients with DM.

DATA SOURCES Data sources included MEDLINE (1966-2012), EMBASE (1988-2012), the Cochrane Central Register of Controlled Trials, conference proceedings, and article reference lists.

STUDY SELECTION We included randomized clinical trials reporting the effects of ACEI and ARB regimens for DM on all-cause mortality, CV deaths, and major CV events with an observation period of at least 12 months. Studies were excluded if they were crossover trials.

DATA EXTRACTION AND SYNTHESIS Dichotomous outcome data from individual trials were analyzed using the risk ratio (RR) measure and its 95% CI with random-effects models. We estimated the difference between the estimates of the subgroups according to tests for interaction. We performed meta-regression analyses to identify sources of heterogeneity.

MAIN OUTCOMES AND MEASURES Primary end points were all-cause mortality and death from CV causes. Secondary end points were the effects of ACEIs and ARBs on major CV events.

RESULTS Twenty-three of 35 identified trials compared ACEIs with placebo or active drugs (32 827 patients) and 13 compared ARBs with no therapy (controls) (23 867 patients). When compared with controls (placebo/active treatment), ACEIs significantly reduced the risk of all-cause mortality by 13% (RR, 0.87; 95% CI, 0.78-0.98), CV deaths by 17% (0.83; 0.70-0.99), and major CV events by 14% (0.86; 0.77-0.95), including myocardial infarction by 21% (0.79; 0.65-0.95) and heart failure by 19% (0.81; 0.71-0.93). Treatment with ARBs did not significantly affect all-cause mortality (RR, 0.94; 95% CI, 0.82-1.08), CV death rate (1.21; 0.81-1.80), and major CV events (0.94; 0.85-1.01) with the exception of heart failure (0.70; 0.59-0.82). Both ACEIs and ARBs were not associated with a decrease in the risk for stroke in patients with DM. Meta-regression analysis showed that the ACEI treatment effect on all-cause mortality and CV death did not vary significantly with the starting baseline blood pressure and proteinuria of the trial participants and the type of ACEI and DM.

CONCLUSIONS AND RELEVANCE Angiotensin-converting enzyme inhibitors reduced all-cause mortality, CV mortality, and major CV events in patients with DM, whereas ARBs had no benefits on these outcomes. Thus, ACEIs should be considered as first-line therapy to limit excess mortality and morbidity in this population.

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Diabetes mellitus (DM) is increasing in prevalence worldwide and afflicts an estimated 6.6% of the global adult population, or approximately 285 million individuals. By 2030, an estimated 350 million people worldwide will be living with DM.[1,2]

As a strong independent risk factor for cardiovascular (CV) disease, DM is associated with many macrovascular complications. It is a leading cause of premature death, and approximately 6.8% of adult deaths worldwide from heart disease or stroke are attributed to DM.[3] Mortality rates from CV disease in patients with DM are 2- to 4-fold higher compared with those in patients without DM.[4-6]

The renin-angiotensin-aldosterone system is a major regulatory system of CV and renal function.[7,8] Thus, multiple clinical trials[9-13] in past decades have confirmed that suppression of renin-angiotensin-aldosterone system activity might be expected to reduce CV mortality and all-cause mortality.

Despite the above findings, however, the cardioprotective effects of renin-angiotensin-aldosterone system blockade were recently called into question. The Non-Insulin-Dependent Diabetes, Hypertension, Microalbuminuria or Proteinuria, Cardiovascular Events, and Ramipril (DIABHYCAR) study[14] found that angiotensin-converting enzyme inhibitors (ACEIs) had no effect on CV events in patients with type 2 DM and albuminuria. There was a higher rate of fatal CV events with olmesartan therapy among patients with type 2 DM in the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study.[15]

The American Diabetes Association[16] recommends that patients with DM and hypertension should be treated with a pharmacologic therapy regimen that includes an ACEI or an angiotensin II receptor blocker (ARB). If one class of medication is not tolerated, the other class of medication should be used. Both types of drugs limit the effects of angiotensin II, but the mechanisms of action are not identical.[17] Thus, theoretically, there might be relevant differences between the drug classes. The recent meta-analysis by van Vark et al[18] showed that ACEIs or ARBs had different effects on all-cause mortality in patients with hypertension. This difference might also exist in the treatment of DM. However, evaluating the relative effects of ACEIs and ARBs is difficult owing to the lack of adequate head-to-head trials. In light of the above, we undertook the present meta-analysis aiming to overcome this limitation by evaluating the effect of ACEIs and ARBs separately vs placebo or other medications on the incidence of all-cause mortality, CV deaths, and CV events in patients with DM.

Methods

Inclusion and Exclusion Criteria

The study was included if it was a randomized clinical trial (RCT), including post hoc analyses and subgroups for DM, with a median or mean follow-up of at least 12 months. The study was included if it compared ACEIs and ARBs (any dose or type) with placebo, no treatment, or other antihypertensive drugs (including ACEIs vs ARBs). The study was excluded if the RCT did not assess the effects of ACEI and ARB regimens for DM on CV deaths or all-cause mortality. Finally, studies were excluded if they were crossover trials.

Search Strategy

We performed a systematic review of the literature in agreement with the approach recommended by the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement for conducting meta-analyses of intervention studies.[19] Electronic searches were performed using MEDLINE (January 1, 1966, to December 31, 2012) and EMBASE (January 1, 1988, to December 31, 2012). The Cochrane Central Register of Controlled Trials was also searched. The following Medical Subject Heading terms and text words were used: *type 2 diabetes*, *type 1 diabetes mellitus* or *DM*, *cardiovascular events* or *mortality*, *myocardial infarction, MI*, *stroke*, *heart failure*, *angiotensin-converting enzyme inhibitors*, *angiotensin II receptor*, *ACE inhibitors*, *ARB*, *angiotensin receptor, angiotensin II receptor blocker*, *cardiovascular death*, *randomized controlled trials*, and *clinical trials*. The search was limited to RCTs with at least 12 months of follow-up, without age or language of publication restrictions. Reference lists from cited articles were also searched. The ClinicalTrials.gov website was searched for randomized trials that were registered as completed but had not yet been published. Abstracts presented at American Diabetic Association meetings from 2005 to 2012 were searched for additional unpublished data.

The titles and abstracts of the articles from these searches were independently analyzed by two of the authors (J. Cheng and W.Z.) to ascertain inclusion criteria conformity. The full text of an article was carefully reviewed if screening of its title and abstract was unclear with regard to its admissibility.

Quality Assessment

We evaluated the quality of the studies included in terms of allocation concealment and of intention-to-treat analysis; blinding of investigators, participants, and outcome assessors; and completeness of follow-up. In addition, we used the Jadad scale to determine the quality of the trials.[20]

End Points

Primary end points were all-cause mortality and death from CV causes. Secondary end points were the effects of ACEIs and ARBs on the occurrence of major CV events, defined as the composite of CV death, nonfatal myocardial infarction (MI) and stroke, congestive heart failure, and coronary artery bypass grafting or percutaneous coronary intervention, in patients with DM, as well as the effects of ACEIs and ARBs on MI, stroke, and congestive heart failure in patients with DM. End point definitions referred to those reported in the originally published articles. Outcomes were based on the longest follow-up period available for each study.

Statistical Analysis

Individual patient data were not available for the studies in this analysis; thus, tabular data were used. Dichotomous outcome data from individual trials were analyzed using the risk ratio (RR) measure and its 95% CI.

To determine the robustness of our pooled effects, we compared our primary analysis with random-effects models.[21] The results were confirmed by the Mantel-Haenszel fixed-effect model to avoid small studies being overly weighted. Funnel plots and the Begg test were used to probe for publication bias. Heterogeneity was assessed among studies using the I^2 statistic, judging values of less than 25% to be minimal, 25% to 49% to be moderate, and 50% or greater to be substantial.

Subgroup Analysis and Meta-regression

Given that the results might be different based on the control group (placebo vs active treatment), we performed the primary analyses after stratifying the studies based on the comparator (placebo vs active treatment). We estimated the difference between the estimates of the subgroups according to tests for interaction.[22] $P < .05$ indicates that the effects of treatment differed significantly between the tested subgroups.

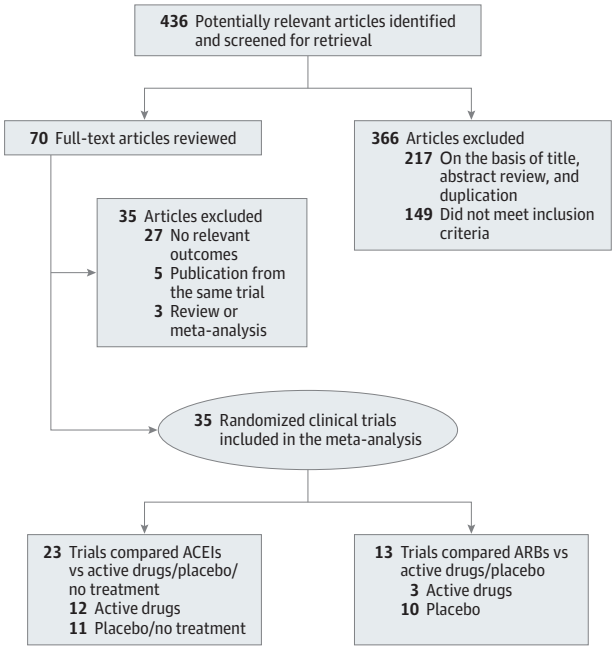
We performed random-effects univariate meta-regression when possible to explore the role of potential sources of heterogeneity related to the participants (ie, age, stage of proteinuria, type of DM, and blood pressure level at baseline), the agent used (different types), and trial quality (allocation concealment and Jadad scale) regarding the effect on the primary end points of the interventions. A 2-sided P value <.05 was considered statistically significant. All statistical analyses were performed using Review Manager, 5.10, statistical software (Cochrane Collaboration)[23] and Stata, version 11 (Stata Corp), for the meta-analysis.

Results

Trial Flow and Study Characteristics

The combined search of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials, which also included some handsearching of relevant nephrology journals, retrieved 436 citations. After discarding several duplicates retrieved by individual searches and reviewing all titles and abstracts, many studies were excluded because they were not RCTs, did not investigate any of the outcomes of interest to this study, or were animal or basic research studies or review articles. Overall, 35 trials (35 with 1 study using both an ACEI and ARB)[12,14,15,24-54] enrolling a total of 56 444 patients were included in this analysis (**Figure 1**). Twenty-three studies (n = 32 827) compared ACEIs with control therapy, and 13 studies (n = 23 867) compared ARBs with control therapy. The 23 comparator arms included 11 arms that compared ACEIs with placebo and 12 arms in which the comparator was active treatment. Of the 13 ARB trials, the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) substudy,[28] Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) study,[51] Diabetics Exposed to Telmisartan and Enalapril (DETAIL) trial,[54] and Irbesartan Diabetic Nephropathy Trial (IDNT)[12] (active substudy) compared ARBs with active drugs, and the remaining studies[15,46-50,52,53] compared ARBs with placebo. The DETAIL trial compared ACEIs with ARBs, so the DETAIL trial was included in the ACEI group and the ARB group.

Figure 1. Flowchart of Article Selection for Meta-analysis



Potentially relevant reports identified and screened for retrieval. ACEIs indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers.

The details of the interventions, baseline characteristics of the populations, study period, concomitant drugs, and follow-up in the RCTs included in our analysis are summarized in **Table 1**.[12,14,15,24-54]

Quality Assessment

The quality of the included studies was assessed independently by 2 of the authors (W.Z. and J. Cheng) using the Jadad score, which ranges from 0 to 5 points. Study quality generally was good. Twenty-one studies (60.0%) had a Jadad score greater than 3 (Table 1). Participants and investigators were blinded in 27 trials. Eighteen of the studies (51.4%) met allocation concealment criteria, and 26 studies (74.3%) met the intention-to-treat analysis criteria.

Primary End Points

Effects of ACEIs on All-Cause Mortality and CV Deaths

A total of 20 studies of 23 RCTs were analyzed to prospectively test the effectiveness of ACEIs for all-cause mortality in a total of 25 544 patients with DM. In the 20 trials combined, ACEIs were associated with a statistically significant 13% reduction in all-cause mortality compared with control therapy (RR, 0.87; 95% CI, 0.78-0.98; $P = .02$) (**Figure 2**). The results were similar when ACEIs were compared with placebo or active treatment ($P = .49$ for interaction). There was low to moderate heterogeneity ($I^2 = 26\%$; $P = .14$) and no evidence of publication bias ($P = .69$) (Supplement [eFigure 1]).

Table 1. Characteristics of Interventions and Populations at Baseline in Included RCTs

Source	No. of Patients, Type of DM	Drugs		Baseline Characteristics					Quality Assessment		
		Treatment	Control	Mean Age, y	Men, %	Hypertension, %	Renal Function, Albuminuria, Mean	Follow-up, mo	Jadad Score	ITT	Allocation Concealment
ACEIs											
J-MIND,[35] 2001	436, Type 2	Enalapril	Nifedipine	60	49	Yes	SCr <2.5 mg/dL, UAE <30 g/d	24	3	Yes	NR
Lewis et al,[25] 1993	409, Type 1	Captopril	Placebo	35	53	75	SCr <2.5mg/dL, UAE >0.5 g/d	36	4	Yes	NR
ABCD study,[33] 1998	470, Type 2	Enalapril	Nisoldipine	57	67	Yes	GFR 87 mL/min	67	5	Yes	Yes
ADVANCE study,[34] 2007	11 140, Type 2	Perindopril	Placebo	66	57	68	SCr 0.98 mg/dL	60	5	Yes	Yes
CAPPP substudy,[29] 2001	572, Type 2	Captopril	Diuretic/ β-blocker	55	62	Yes	...	60	4	Yes	NR
FACET study,[31] 1998	380, Type 2	Fosinopril	Amlodipine	63	64	Yes	...	42	3	Yes	NR
HOPE substudy,[30] 2000	3577, Type 2	Ramipril	Placebo	55	62	54	...	60	5	Yes	Yes
JMIC-B substudy,[27] 2004	372, Type 2	ACEI	Nifedipine	63	69	Yes	...	36	3	Yes	NR
UKPDS 39,[32] 1998	758, Type 2	Captopril	Atenolol	56	54	Yes	...	108	3	Yes	Yes
PERSUADE substudy,[26] 2005	1502, Type 2	Perindopril	Placebo	62	82	39.5	...	52	5	Yes	Yes
Fogari et al,[37] 2002	205, Type 2	Fosinopril	Amlodipine	62	58	Yes	SCr <1.5 mg/dL, UAE 30-300 µg/min	48	2	No	NR
Ravid et al,[38] 1998	156, Type 1	Enalapril	Placebo	55	48	No	SCr <1.39 mg/dL	72	3	No	NR
DIABHYCAR study,[14] 2004	4912, Type 2	Ramipril	Placebo	65	70	55	SCr <1.7 mg/dL, UAE ≥20 µg/min	48	5	Yes	Yes
ALLHAT study,[36] 2000	6635, Mixed	Lisinopril	Amlodipine	63	55	Yes	GFR (mean) 102 mL/min; UAE 961 mg/24 h	36	5	Yes	Yes
Nielsen et al,[39] 1997	36, Type 2	Lisinopril	Atenolol	61	75	Yes	...	36	2	No	NR
Bakris et al,[40] 1996	34, Type 2	Lisinopril	Atenolol	62	50	Yes	GFR <70 mL/min, UAE >2.0 g/24 h	72	2	No	NR
Bauer et al,[41] 1992	33, Mixed	Enalapril	Placebo	57	73	66.7	UAE >0.5 g/d	18	2	No	NR
Laffel et al,[42] 1995	103, Type 1	Captopril	Placebo	32	71	No	SCr 1.1 mg/dL, UAE 20-200 µg/min	36	3	No	NR
Nankervis et al,[43] 1998	40, Mixed	Perindopril	Placebo	43	80	42.5	SCr <1.36 mg/dL, UAE 20-200 µg/min	36	3	No	NR
Parving et al,[44] 1989	32, Type 1	Captopril	No treatment	30	72	No	SCr <1.36 mg/ dL, UAE >300 mg/24 h	12	2	No	NR
STOP Hypertension-2 study,[24] 2000	719, Type 2	ACEIs	Diuretic/ β-blocker	76	40	Yes	...	48	5	Yes	Yes
Sano et al,[45] 1994	56, Type 1	Enalapril	No treatment	62		No	SCr <1.36 mg/dL, 20-300 mg/24 h	48	2	No	NR
ARBs											
CASE-J study,[51] 2010	2018, Type 2	Candesartan	Amlodipine	63	56	Yes	...	38	3	Yes	NR
PRoFESS study,[52] 2008	5743, Type 2	Telmisartan	Placebo	66	65	74	...	30	4	Yes	NR
SCOPE study,[53] 2005	599, Type 2	Candesartan	Placebo	75	40	Yes	...	44	4	Yes	NR

(continued)

Table 1. Characteristics of Interventions and Populations at Baseline in Included RCTs (continued)

Source	No. of Patients, Type of DM	Drugs		Baseline Characteristics					Quality Assessment		
		Treatment	Control	Mean Age, y	Men, %	Hypertension, %	Renal Function, Albuminuria, Mean	Follow-up, mo	Jadad Score	ITT	Allocation Concealment
RENAAL study,[46] 2001	1513, Type 2	Losartan	Placebo	60	63	Yes	SCR 1.3-3.0 mg/dL, UAE >0.5 g/24 h	41	5	Yes	Yes
IDNT study,[12] 2001	1715, Type 2	Irbesartan	Placebo/ amlodipine	59	68	Yes	SCR 1.0-3.0 mg/dL, UAE >0.9 g/24 h	31	5	Yes	Yes
ORIENT study,[47] 2011	566, Type 2	Olmesartan	Placebo	59	69	Yes	SCr <2.5 mg/ dL, UAE >300 µg/min	38	5	Yes	Yes
ROADMAP study,[15] 2011	4447, Type 2	Olmesartan	Placebo	57	46	90	GFR>30 mL/min	38	5	Yes	Yes
IRMA study,[48] 2001	590, Type 2	Irbesartan	Placebo	58	68	Yes	SCr <1.5 mg/dL	24	5	Yes	Yes
LIFE substudy,[28] 2002	1195, Type 2	Losartan	Atenolol	67	47	Yes	...	56	5	Yes	Yes
DIRECT-Prevent 1,[49] 2009	1421, Type 1	Candesartan	Placebo	29	56	No	SCr <1.5 mg/ dL, UAE <20 µg/min	56	5	Yes	Yes
DIRECT-Protect 1[49] 2009	1905, Type 1	Candesartan	Placebo	29	57	No	SCr <1.5 mg/ dL, UAE <20 µg/min	56	5	Yes	Yes
DIRECT-Protect 2,[50] 2008	1905, Type 2	Candesartan	Placebo	40	50	62	SCr <1.5 mg/ dL, UAE <20 µg/min	56	5	Yes	Yes
DETAIL study,[54] 2004	250, Type 2	Telmisartan	Enalapril	61	72	Yes	GFR 91 mL/min	60	5	Yes	Yes

Abbreviations: ABCD, Appropriate Blood Pressure Control in Diabetes; ACEIs, angiotensin-converting enzyme inhibitors; ADVANCE, Action in Diabetes and Vascular disease: Preterax and Diamicron-MR Controlled Evaluation; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ARBs, angiotensin II receptor blockers; CAPPP, Captopril Prevention Project; CASE-J, Candesartan Antihypertensive Survival Evaluation in Japan; DETAIL, Diabetics Exposed to Telmisartan and Enalapril; DIABHYCAR, Non–Insulin-Dependent Diabetes, Hypertension, Microalbuminuria or Proteinuria, Cardiovascular Events, and Ramipril; DIRECT-Prevent, Diabetic Retinopathy Candesartan Trials—Prevent; DIRECT-Protect, Diabetic Retinopathy Candesartan Trials–Protect; DM, diabetes mellitus; ellipses, information not reported; FACET, Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial; GFR, glomerular filtration rate; HOPE, Heart Outcomes Prevention Evaluation; IDNT, Irbesartan Diabetic Nephropathy Trial; IRMA, Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria; ITT, intention-to-treat; JMIC-B, Japan Multicenter Investigation for Cardiovascular Diseases–B; J-MIND, Japan Multicenter Investigation of Antihypertensive Treatment for Nephropathy in Diabetics; LIFE, Losartan Intervention for Endpoint Reduction in Hypertension; NR, not reported; ORIENT, Olmesartan Reducing Incidence of Endstage Renal Disease in Diabetic Nephropathy Trial; PERSUADE, Effect of Perindopril on Cardiovascular Morbidity and Mortality in Patients With Diabetes in the EUROPA Study; PROFESS, Prevention Regimen for Effectively Avoiding Second Strokes; RCTs, randomized clinical trials; RENAAL, Reduction of Endpoints in Non–Insulin-Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention; SCOPE, Study on Cognition and Prognosis in the Elderly; SCr, serum creatinine; STOP-Hypertension–2, Swedish Trial in Old Patients With Hypertension–2; UAE, urinary albumin excretion; UKPDS 39, United Kingdom Prospective Diabetes Study 39.

SI unit conversion factor: To convert SCr to micromoles per liter, multiply by 88.4.

Thirteen studies of 23 RCTs assessed the effect of ACEI therapy on the occurrence of CV deaths in 24 334 patients with DM. According to our meta-analysis, in which the weight of individual studies was taken into account, ACEIs were associated with a significant 17% reduction in CV deaths compared with control therapy (RR, 0.83; 95% CI 0.70-0.99; P = .04). In addition, the results were similar when ACEIs were compared with placebo or active treatment (P = .96 for interaction). For the outcome of CV deaths, there was moderate heterogeneity (I^2 = 40%; P = .07), but no evidence of publication bias (P = .51) (Supplement [eFigure 2]).

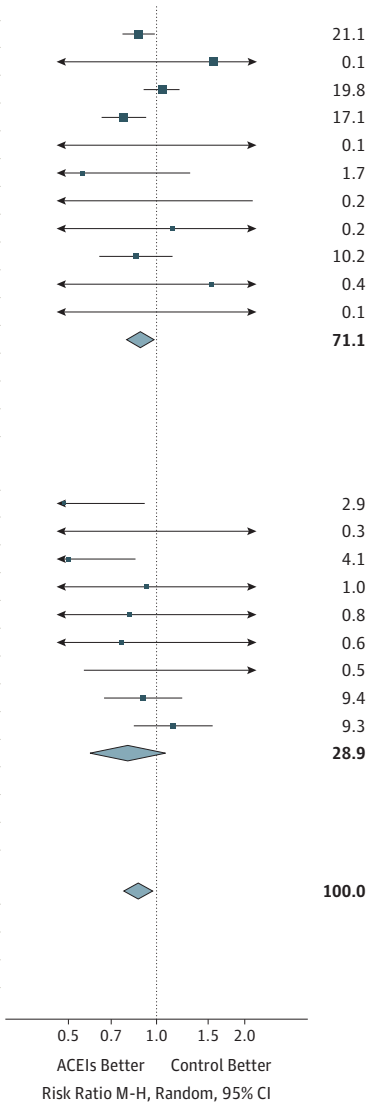
Effects of ARBs on All-Cause Mortality and CV Deaths

Eleven studies involving 17 334 patients have been published on the effect of ARB therapy on all-cause mortality in patients with DM. There was no significant decrease in the risk of total mortality when ARB therapy was compared with control therapy in patients with DM (RR, 0.94; 95% CI 0.82-1.08; P = .39) (**Figure 3**). The results were similar when ARBs were compared with placebo or active treatment (P = .16 for interaction). Heterogeneity among the trials was low to moderate for all-cause mortality (P = .23; I^2 = 22%). The active control group (I^2 = 49%) was mainly derived from the LIFE study.[28] After excluding the LIFE study (losartan), greater heterogeneity disappeared (RR, 0.96; 95% CI, 0.77-1.20; I^2 = 0%).

Seven studies assessed the effect of ARB therapy on the occurrence of CV deaths in 10 801 patients with DM. According to our meta-analysis, in which the weight of individual studies was taken into account, ARB treatment did not significantly reduce the risk for CV deaths compared with con-

Figure 2. Angiotensin-Converting Enzyme Inhibitors (ACEIs) and All-Cause Mortality Stratified by Comparison Group (Placebo vs Active)

Study or Subgroup	ACEIs Events	ACEIs Total	Control Events	Control Total	Risk Ratio M-H, Random, 95% CI	Weight, %
Placebo						
ADVANCE study,[34] 2007	408	5569	471	5571	0.87 (0.76-0.98)	21.1
Bauer et al,[41] 1992	1	18	0	15	2.53 (0.11-57.83)	0.1
DIABHYCAR study,[14] 2004	334	2443	324	2469	1.04 (0.90-1.20)	19.8
HOPE study,[30] 2000	196	1808	248	1769	0.77 (0.65-0.92)	17.1
Laffel et al,[42] 1995	1	70	0	73	3.13 (0.13-75.49)	0.1
Lewis et al,[25] 1993	8	207	14	202	0.56 (0.24-1.30)	1.7
Nankervis et al,[43] 1998	0	17	3	14	0.12 (0.01-2.13)	0.2
Parving et al,[44] 1989	1	15	1	17	1.13 (0.08-16.59)	0.2
PERSUADE substudy,[26] 2005	73	721	93	781	0.85 (0.64-1.14)	10.2
Ravid et al,[38] 1998	3	77	2	79	1.54 (0.26-8.96)	0.4
Sano et al,[45] 1994	1	31	0	31	3.00 (0.13-70.92)	0.1
Subtotal		**10976**		**11021**	**0.89 (0.79-0.99)**	**71.1**
Total Events	**1026**		**1156**			
Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 12.47$, $df = 10$, $P = .25$; $I^2 = 20\%$						
Test for overall effect: $Z = 2.13$, $P = .03$						
Active						
ABCD study,[33] 1998	13	235	27	235	0.48 (0.25-0.91)	2.9
Bakris et al,[40] 1996	1	18	5	34	0.38 (0.05-2.99)	0.3
CAPPP study,[29] 2001	20	309	34	263	0.50 (0.30-0.85)	4.1
DETAIL study,[54] 2004	6	130	6	120	0.92 (0.31-2.78)	1.0
FACET study,[31] 1998	4	189	5	191	0.81 (0.22-2.96)	0.8
Fogari et al,[37] 2002	3	102	4	103	0.76 (0.17-3.30)	0.6
JMIC-B study,[27] 2004	5	173	2	199	2.88 (0.57-14.64)	0.5
STOP-2 substudy,[24] 2000	56	235	67	253	0.90 (0.66-1.22)	9.4
UKPDS 39 study,[32] 1998	75	400	59	358	1.14 (0.83-1.55)	9.3
Subtotal		**1791**		**1756**	**0.80 (0.60-1.08)**	**28.9**
Total Events	**183**		**209**			
Heterogeneity: $\tau^2 = 0.06$; $\chi^2 = 13.26$, $df = 8$, $P = .10$; $I^2 = 40\%$						
Test for overall effect: $Z = 1.45$, $P = .15$						
Total		**12767**		**12777**	**0.87 (0.78-0.98)**	**100.0**
Total Events	**1209**		**1365**			
Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 25.79$, $df = 19$, $P = .14$; $I^2 = 26\%$						
Test for overall effect: $Z = 2.38$, $P = .02$						



Diamond indicates the overall summary estimate for the analysis (width of the diamond represents the 95% CI); boxes, the weight of individual studies in the pooled analysis. Trials to the left of the vertical line showed a reduction in risk with the experimental intervention; those to the right showed an increase in risk with the experimental intervention. M-H indicates Mantel-Haenszel. See Table 1 footnote for expansion of clinical trial acronyms.

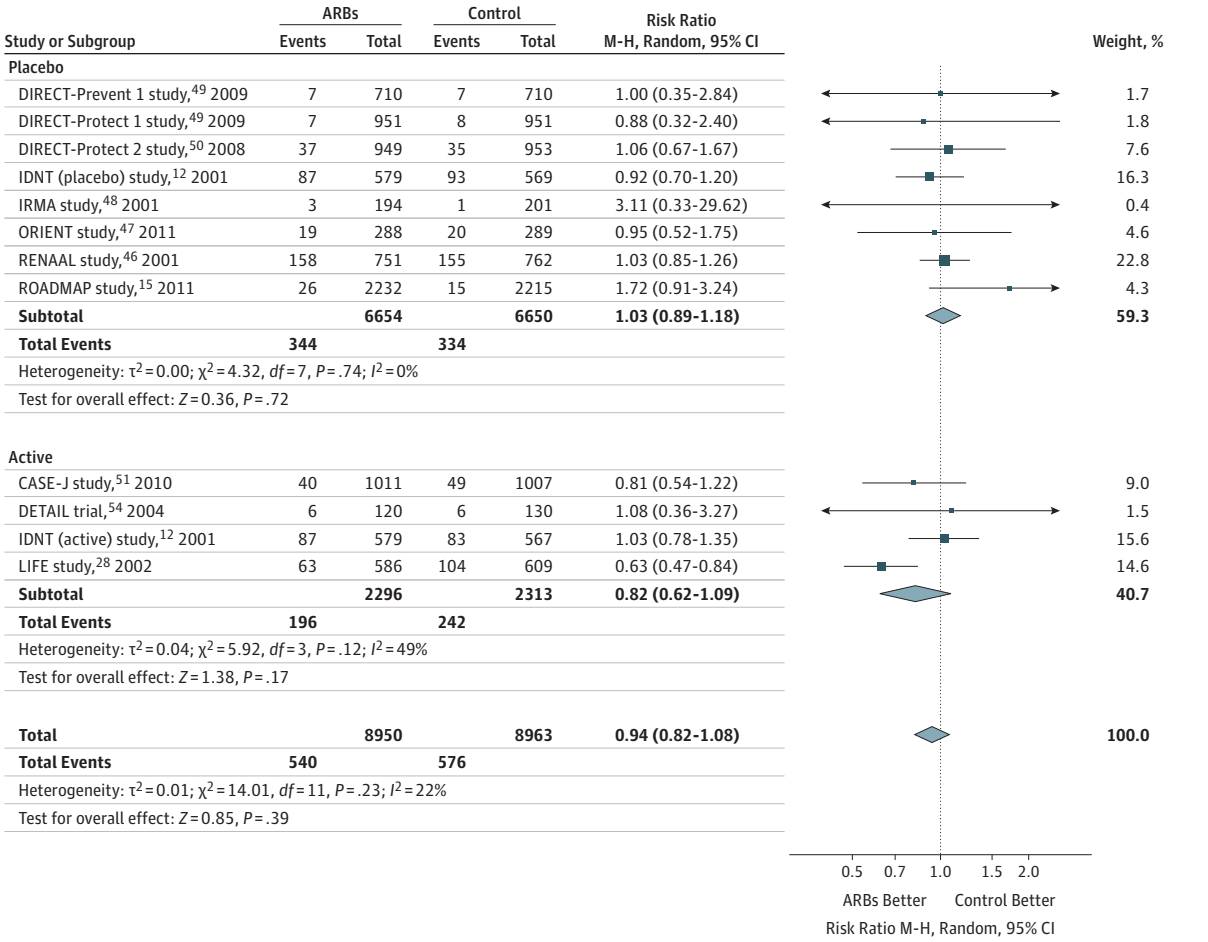
trol therapy (RR, 1.21; 95% CI, 0.81-1.80; P = .35). In addition, the results were similar when ARBs were compared with placebo or active treatment (P = .12 for interaction). However, the degree of heterogeneity in the treatment effect across all trials was significant (P = .01; I^2 = 61%). The ROADMAP study[15] and the Olmesartan Reducing Incidence of Endstage Renal Disease in Diabetic Nephropathy Trial (ORIENT)[47] used olmesartan as a treatment drug. After exclusion of 2 trials involving olmesartan, heterogeneity among the trials was not significantly different (I^2 = 41%; RR, 0.98). When olmesartan treatment was compared with placebo, there was a significant increase in the risk for CV deaths (2 trials, 5024 patients; RR, 4.10; 95% CI, 1.68-9.98; P = .002). When ARB therapy was compared with control therapy in patients with DM, there was no evidence of publication bias for the outcomes of all-cause mortality (P = .50) (Supplement [eFigure 3]) and CV deaths (P = .23) (Supplement [eFigure 4]).

Secondary End Points

Effects of ACEIs on Major CV Events and Cause-Specific CV Outcomes

Fourteen studies assessed the effect of ACEI therapy on the occurrence of major CV events in 34 352 patients. Drugs from this

Figure 3. Angiotensin II Receptor Blockers (ARBs) and All-Cause Mortality Stratified by Comparison Group (Placebo vs Active)



Diamond indicates the overall summary estimate for the analysis (width of the diamond represents the 95% CI); boxes, the weight of individual studies in the pooled analysis. Trials to the left of the vertical line showed a reduction in risk with the experimental intervention; those to the right showed an increase in risk with the experimental intervention. M-H indicates Mantel-Haenszel. See Table 1 footnote for expansion of clinical trial acronyms.

class significantly reduced the risk of major CV events by 14% (RR, 0.86; 95% CI, 0.77-0.95) (Supplement [eFigure 5]) compared with control therapy. Heterogeneity between trials was significant for all CV events (P = .003; I^2 = 59%). Subgroup analysis showed that heterogeneity was mainly derived from the active control group (I^2 = 65%); the results were similar when ACEIs were compared with either placebo or active treatment (P = .31 for the interaction).

Myocardial infarction was reported in 11 trials including 22 741 participants, among whom 1944 events were observed. Therapy with ACEIs reduced the risk of myocardial infarction by 21% (RR, 0.79; 95% CI, 0.65-0.95; P = .01) (**Figure 4**A). Eleven trials (33 508 participants) reported 1775 stroke events, and 8 trials (12 651 participants) reported 782 occurrences of heart failure. Therapy with ACEIs was associated with a 19% lower risk of heart failure (RR, 0.81; 95% CI, 0.71-0.93; P = .002) (Figure 4B), but there was no clearly apparent beneficial effect for stroke (0.95; 0.86-1.04; P = .28) (Figure 4C).

Effects of ARBs on Major CV Events and Cause-Specific CV Outcomes

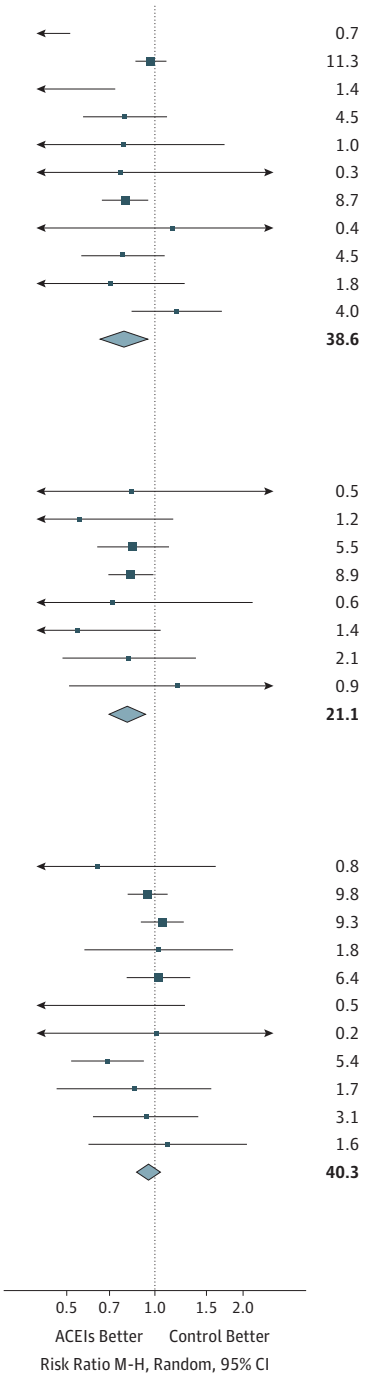
Data regarding the effects of ARBs on major CV events were available from 9 trials that included 18 743 participants and reported 2992 major CV events. With all trials combined, there was no significant decrease in the risk of major CV events (RR, 0.94; CI 0.85-1.01; P = .07) (Supplement [eFigure 6]). No significant heterogeneity existed between trials for these end points (P = .32; I^2 = 13%). The results were similar when ARBs were compared with placebo or active treatment (P = .33 for the interaction).

Six trials (11 454 participants) reported 415 myocardial infarction events, and 8 trials (17 796 participants) reported 1064 occurrences of stroke. There were no clearly apparent beneficial effects for myocardial infarction (RR, 0.89; 95% CI, 0.74-1.07; P = .22; I^2 = 0%) (**Figure 5**A) and stroke (1.00; 0.89-1.12; P = .94; I^2 = 0%) (Figure 5B).

Heart failure was reported by 4 trials that included 4989 participants, among whom 571 events were observed.

Figure 4. Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Cause-Specific Cardiovascular Outcomes

	Study or Subgroup	ACEIs Events	ACEIs Total	Control Events	Control Total	Risk Ratio M-H, Random, 95% CI	Weight, %
A	**Myocardial infarction**						
	ABCD study,[33] 1998	5	235	25	235	0.20 (0.08-0.51)	0.7
	ALLHAT study,[36] 2000	362	3510	638	5994	0.97 (0.86-1.09)	11.3
	CAPPP study,[29] 2001	12	309	27	263	0.38 (0.20-0.73)	1.4
	DIABHYCAR study,[14] 2004	61	2443	78	2469	0.79 (0.57-1.10)	4.5
	FACET study,[31] 1998	10	189	13	191	0.78 (0.35-1.73)	1.0
	Fogari et al,[37] 2002	3	102	4	104	0.76 (0.18-3.33)	0.3
	HOPE study,[30] 2000	185	1808	229	1769	0.79 (0.66-0.95)	8.7
	JMIC-B study,[27] 2004	4	173	4	199	1.15 (0.29-4.53)	0.4
	PERSUADE substudy,[26] 2005	56	721	78	781	0.78 (0.56-1.08)	4.5
	STOP-2 substudy,[24] 2000	17	235	26	253	0.70 (0.39-1.26)	1.8
	UKPDS 39 study,[32] 1998	61	400	46	358	1.19 (0.83-1.69)	4.0
	Subtotal		**10125**		**12616**	**0.79 (0.65-0.95)**	**38.6**
	Total Events	**776**		**1168**			
	Heterogeneity: $\tau^2=0.04$; $\chi^2=24.04$, $df=10$, $P=.007$; $I^2=58\%$						
	Test for overall effect: $Z=2.51$, $P=.01$						
B	**Heart failure**						
	ABCD study,[33] 1998	5	235	6	235	0.83 (0.26-2.69)	0.5
	CAPPP study,[29] 2001	11	309	17	236	0.55 (0.26-1.15)	1.2
	DIABHYCAR study,[14] 2004	85	2443	102	2469	0.84 (0.64-1.12)	5.5
	HOPE study,[30] 2000	198	1808	234	1769	0.83 (0.69-0.99)	8.9
	JMIC-B study,[27] 2004	5	173	8	199	0.72 (0.24-2.16)	0.6
	PERSUADE substudy,[26] 2005	13	721	26	781	0.54 (0.28-1.05)	1.4
	STOP-2 substudy,[24] 2000	22	235	29	253	0.82 (0.48-1.38)	2.1
	UKPDS 39 study,[32] 1998	12	4000	9	358	1.19 (0.51-2.80)	0.9
	Subtotal		**6324**		**6327**	**0.81 (0.71-0.93)**	**21.1**
	Total Events	**351**		**431**			
	Heterogeneity: $\tau^2=0.00$; $\chi^2=3.46$, $df=7$, $P=.84$; $I^2=0\%$						
	Test for overall effect: $Z=3.05$, $P=.002$						
C	**Stroke**						
	ABCD study,[33] 1998	7	235	11	235	0.64 (0.25-1.61)	0.8
	ADVANCE study,[34] 2007	286	5569	303	5571	0.94 (0.81-1.11)	9.8
	ALLHAT study,[36] 2000	206	3510	332	5994	1.06 (0.90-1.25)	9.3
	CAPPP study,[29] 2001	23	309	19	263	1.03 (0.57-1.85)	1.8
	DIABHYCAR study,[14] 2004	118	2443	116	2469	1.03 (0.80-1.32)	6.4
	FACET study,[31] 1998	4	189	10	191	0.40 (0.13-1.27)	0.5
	Fogari et al,[37] 2002	2	102	2	103	1.01 (0.15-7.03)	0.2
	HOPE study,[30] 2000	76	1808	108	1769	0.69 (0.52-0.92)	5.4
	PERSUADE substudy,[26] 2005	18	721	23	781	0.85 (0.46-1.56)	1.7
	STOP-2 substudy,[24] 2000	34	235	39	253	0.94 (0.61-1.43)	3.1
	UKPDS 39 study,[32] 1998	21	400	17	358	1.11 (0.59-2.06)	1.6
	Subtotal		**15521**		**17987**	**0.95 (0.86-1.04)**	**40.3**
	Total Events	**795**		**980**			
	Heterogeneity: $\tau^2=0.00$; $\chi^2=10.17$, $df=10$, $P=.43$; $I^2=2\%$						
	Test for overall effect: $Z=1.09$, $P=.28$						



Diamond indicates the overall summary estimate for the analysis (width of the diamond represents the 95% CI); boxes, the weight of individual studies in the pooled analysis. Trials to the left of the vertical line showed a reduction in risk with the experimental intervention; those to the right showed an increase in risk with the experimental intervention. M-H indicates Mantel-Haenszel. See Table 1 footnote for expansion of clinical trial acronyms.

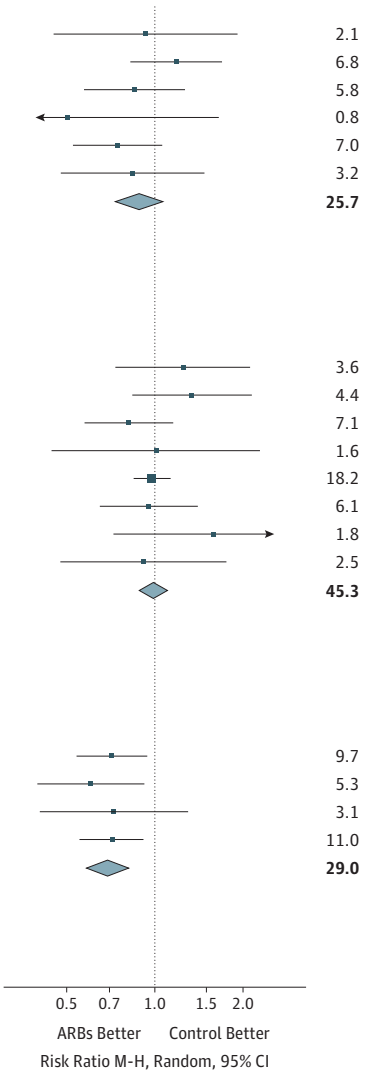
Therapy with ARBs reduced the risk of heart failure by 30% (RR, 0.70; CI, 0.59-0.82; $P < .01$; $I^2 = 0\%$) (Figure 5C). No significant heterogeneity existed between trials for these end points.

Meta-regression

There was no evidence that the observed effects of ACEIs on all-cause mortality and CV deaths differed among trial subgroups defined according to a broad range of baseline charac-

Figure 5. Angiotensin II Receptor Blockers (ARBs) and Cause-Specific Cardiovascular (CV) Outcomes

	ARBs		Control		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	Weight, %
A Myocardial infarction						
CASE-J study,[51] 2010	14	1011	15	1007	0.93 (0.45-1.92)	2.1
IDNT study,[12] 2001	44	579	73	1136	1.18 (0.82-1.70)	6.8
LIFE study,[28] 2002	41	586	50	609	0.85 (0.57-1.27)	5.8
ORIENT study,[47] 2011	4	282	8	284	0.50 (0.15-1.65)	0.8
RENAAL study,[46] 2001	50	751	68	762	0.75 (0.53-1.06)	7.0
ROADMAP study,[15] 2011	22	2232	26	2215	0.84 (0.48-1.48)	3.2
Subtotal		**5441**		**6013**	**0.89 (0.74-1.07)**	**25.7**
Total Events	**175**		**240**			
Heterogeneity: $\tau^2=0.00$; $\chi^2=4.34$, $df=5$, $P=.50$; $I^2=0\%$						
Test for overall effect: $Z=1.21$, $P=.22$						
B Stroke						
CASE-J study,[51] 2010	30	1011	24	1007	1.25 (0.73-2.11)	3.6
IDNT study,[12] 2001	28	579	41	1136	1.34 (0.84-2.14)	4.4
LIFE study,[28] 2002	51	586	65	609	0.82 (0.58-1.16)	7.1
ORIENT study,[47] 2011	11	282	11	284	1.01 (0.44-2.29)	1.6
PROFESS study,[52] 2008	316	2840	330	2903	0.98 (0.85-1.13)	18.2
RENAAL study,[46] 2001	47	751	50	762	0.95 (0.65-1.40)	6.1
ROADMAP study,[15] 2011	16	2232	10	2215	1.59 (0.72-3.49)	1.8
SCOPE study,[53] 2005	17	313	17	286	0.91 (0.48-1.76)	2.5
Subtotal		**8594**		**9202**	**1.00 (0.89-1.12)**	**45.3**
Total Events	**516**		**548**			
Heterogeneity: $\tau^2=0.00$; $\chi^2=5.00$, $df=7$, $P=.66$; $I^2=0\%$						
Test for overall effect: $Z=0.08$, $P=.94$						
C Heart Failure						
IDNT study,[12] 2001	60	579	165	1136	0.71 (0.54-0.94)	9.7
LIFE study,[28] 2002	32	586	55	609	0.60 (0.40-0.92)	5.3
ORIENT study,[47] 2011	18	282	25	284	0.73 (0.40-1.30)	3.1
RENAAL study,[46] 2001	89	751	127	762	0.71 (0.55-0.91)	11.0
Subtotal		**2198**		**2791**	**0.70 (0.59-0.82)**	**29.0**
Total Events	**199**		**372**			
Heterogeneity: $\tau^2=0.00$; $\chi^2=0.51$, $df=3$, $P=.92$; $I^2=0\%$						
Test for overall effect: $Z=4.35$, $P<.001$						



Diamond indicates the overall summary estimate for the analysis (width of the diamond represents the 95% CI); boxes, the weight of individual studies in the pooled analysis. Trials to the left of that line showed a reduction in risk with the experimental intervention; those to the right showed an increase in risk with the experimental intervention. M-H indicates Mantel-Haenszel. See Table 1 footnote for expansion of clinical trial acronyms.

teristics, such as age, starting baseline blood pressure, and type of DM (all $P > .05$ for heterogeneity) (**Table 2**). In particular, univariate meta-regression of ACEI treatment on all-cause mortality and CV death outcomes did not vary by the starting baseline blood pressure of the trial participants and the type of ACEI.

Discussion

This meta-analysis of data from 35 RCTs showed that ACEIs and ARBs have different effects on all-cause mortality, CV deaths, and CV events for patients with DM. According to this meta-analysis, ACEIs significantly reduced the risk of all-cause mortality by approximately 13% and CV deaths by approximately 17%. In contrast, ARB treatment did not significantly affect all-cause mortality and CV death. Angiotensin-converting enzyme inhibitors significantly reduced the risk of major CV events by 14%, including myocardial infarction by 21% and heart failure by 19%. There was no significant decrease in the risk of major CV events and myocardial infarction when ARB therapy was compared with control therapy in patients with DM. However, ARB therapy was associated with a 30% reduction in the risk of heart failure. Both ACEIs and ARB agents were not associated with a decrease in the risk for stroke in patients with DM. The results were similar when ACEIs and ARBs were compared with placebo or active treatment for all-cause mortality and CV death outcomes ($P > .05$ for interaction for all comparisons).

Table 2. Univariate Meta-regression Analysis of Potential Sources of Heterogeneity on Effect of ACEIs on All-Cause Mortality and CV Deaths

			ACEI Effects							
			All-Cause Mortality				CV Death			
Model	Covariate	Classification	No. of Studies	RR (95% CI)	*P* Value for Heterogeneity	Heterogeneity Explained by Covariate, %	No. of Studies	RR (95% CI)	*P* Value for Heterogeneity	Heterogeneity Explained by Covariate, %
1	Age, y	<60	10	0.75 (0.57-0.98)	.16	6.95	4	0.73 (0.47-1.14)	.27	35.54
		≥60	10	0.93 (0.85-1.01)			9	0.90 (0.78-1.03)		
2	Type of diabetes	1	5	0.81 (0.40-1.62)	.88	3.77	0			
		2	15	0.86 (0.76-0.99)			13			
3	Type of ACEI		20	0.97 (0.87-1.07)	.47	48.06	13	0.96 (0.82-1.13)	.61	54.37
4	Proteinuria	NR	14	0.84 (0.74-0.95)	.25	49.57	10	0.80 (0.67-0.96)	.42	21.14
		Proteinuria	6	1.00 (0.81-1.24)			3	0.56 (0.16-1.91)		
5	Type of control groups	Placebo	11	0.89 (0.79-0.99)	.89	43.88	4	0.82 (0.67-1.02)	.69	16.70
		CCB	4	0.75 (0.38-1.48)			4	0.61 (0.24-1.53)		
		Diuretic and/or β-blocker	4	0.82 (0.56-1.20)			4	0.86 (0.54-1.37)		
6	Allocation concealment	Adequate	9	0.88 (0.78-1.00)	.30	26.36	8	0.86 (0.72-1.03)	.20	4.12
		Unclear	11	0.68 (0.46-1.02)			5	0.52 (0.27-1.01)		
7	Jadad score	<3	5	0.88 (0.33-2.35)	.98	2.45	3	0.27 (0.07-1.07)	.14	2.22
		≥3	15	0.86 (0.75-0.98)			10	0.85 (0.71-1.02)		
8	Baseline systolic BP	<140	7	0.85 (0.65-1.11)	.73	45.36	1	0.85 (0.59-1.23)	.81	32.09
		140-159	9	0.89 (0.75-1.06)			8	0.84 (0.66-1.08)		
		≥160	4	0.75 (0.54-1.03)			3	0.82 (0.58-1.17)		
9	Baseline diastolic BP	<90	13	0.91 (0.81-1.03)	.18	37.96	6	0.82 (0.66-1.02)	.90	22.82
		90-99	6	0.66 (0.46-0.93)			6	0.83 (0.55-1.26)		
		≥100	1	0.76 (0.17-3.30)			1	0.76 (0.17-3.30)		

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; BP, blood pressure; CCB, calcium channel blocker; CV, cardiovascular; NR, not reported; RR, risk ratio.

Evidence-based recommendations for the management of patients with DM and overt nephropathy using ACEIs or ARBs have been published,[55-58] and the data of the trials suggest that the value of ACEIs or ARB treatment in patients with DM remains controversial or uncertain. A previous meta-analysis by Nakao et al[58] showed that treatment with renin-angiotensin system blockade can routinely be considered for patients with DM to reduce major CV events. Another meta-analysis[59] concluded that renin-angiotensin system blockade, calcium channel antagonists, and diuretics provide no difference in CV protection in patients with specific underlying conditions. Regarding DM and overt nephropathy, these reviews pooled studies with mixed renin-angiotensin-aldosterone system inhibitors, ACEIs, and ARBs. Some reviews focused on the heterogeneity between ACEIs and ARBs for new-onset diabetic kidney disease[60] and hypertension.[18] Few reviews focused on the heterogeneity between ACEIs and ARBs for all-cause mortality and CV death outcomes in patients with DM. The clinical importance of these differences for CV protection was confirmed in our study; unlike ARBs, ACEIs significantly reduced all-cause mortality, CV deaths, and CV events, including myocardial infarction, compared with controls.

A meta-regression analysis is a reasonable method by which to investigate whether potential effect modifiers explain any of the heterogeneity of treatment effects between studies. Meta-regression should generally not be considered when there are fewer than 10 studies in a meta-analysis.[23] Thus, our meta-regression and subgroup analyses were possible only in trials comparing ACEIs with controls for the benefit of this drug class in all-cause mortality and CV deaths; however, all other outcomes involving ARBs were reported in too few trials for the analysis to be robust. There was no evidence that the observed effects varied by older age, hypertension, a history of proteinuria, and the type of ACEIs and DM. Angiotensin-converting enzyme inhibitors might have particular benefits for diabetic pathophysiologic conditions. A possible biological rationale for the benefit of ACEIs, but not ARBs, on cardioprotective effects seems to be related to angiotensin-(1-7) and bradykinin antagonism.[8,17] These two factors occur with ACEIs but not ARBs, and the selectivity of ARBs might not necessarily be an advantage. In the present study considering ARB treatment, there was significant heterogeneity for CV deaths in patients with DM (I^2 = 61%). According to our research, ARB therapy was associated with a trend to more fatal CV events compared with placebo (RR, 1.90). This heterogeneity was at-

tributed mainly to the LIFE substudy[28] and 2 trials using olmesartan.[15,47] The LIFE substudy showed that losartan was more effective than atenolol in reducing CV morbidity and mortality as well as all-cause mortality in patients with DM. Heterogeneity attributed to the LIFE substudy may be closely related to its design and the post hoc observations. On the contrary, olmesartan treatment in the ORIENT study[47] and ROADMAP study[15] showed a significant increase in the risk for CV deaths (RR, 4.22) in patients with DM. The results revealed that heterogeneity may exist among the different ARBs.

Diabetes mellitus is a strong independent risk factor for CV disease. Mortality rates associated with CV disease in patients with DM are 2- to 4-fold higher compared with those in patients without DM, depending on CV comorbidities.[4] Because of the high mortality rates for DM patients, ACEIs should be used as first-line treatment in this population. DETAIL[54] was the only trial comparing CV outcomes in participants with DM randomized to an ACEI or an ARB. There were 21 fatal or nonfatal major CV events among 130 participants receiving enalapril (16.2%) vs 27 events among 120 patients receiving telmisartan (22.5%). No statistics were provided to show whether this difference was statistically significant. However, the results of the trial were consistent with results of the present meta-analysis.

There are several limitations of our analysis. First, the major limitation was the indirect nature of the comparison between ACEIs and ARBs. Second, there was much variation between the studied populations. For example, trials used different ACEIs or ARBs, different target blood pressure and hemoglobin A_{1c} levels were used, different dosages of the active and control drug were used, and there were different follow-up times and background therapies. Finally, trials of ACEIs and ARBs were not equivalent. The ACEI group included more studies (23 vs 13) and more of the population (32 827 vs 23 867). In addition, the characteristics of populations enrolled in ACEI and ARB trials were different. More DM patients with coronary or other vascular atherosclerotic disease were included in ACEI trials than in ARB trials. The main assumption underpinning the validity of network meta-analysis is that there are no important variations between the trials that are making different comparisons other than the treatments being compared.[61] Current hierarchies of evidence tend to place network meta-analysis below direct evidence because indirect comparisons may have biases similar to those in observational studies.[62] The Canadian Agency for Drugs and Technologies in Health[63] allows network meta-analysis only as a sensitivity or supportive analysis to supplement direct evidence. For these reasons, we believe that results from network meta-analysis involving ACEI and ARB treatment may lead to greater clinical heterogeneity and even mislead the reader. Therefore, this meta-analysis cannot confirm that ACEIs are superior to ARBs on survival in patients with DM.

Conclusions

Our meta-analysis shows that ACEIs reduce all-cause mortality, CV mortality, and major CV events in patients with DM, whereas ARBs have no beneficial effects on these outcomes. Thus, ACEIs should be considered as first-line therapy to limit the excess mortality and morbidity in this population.

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Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial

*ADVANCE Collaborative Group**

Summary

Background Blood pressure is an important determinant of the risks of macrovascular and microvascular complications of type 2 diabetes, and guidelines recommend intensive lowering of blood pressure for diabetic patients with hypertension. We assessed the effects of the routine administration of an angiotensin converting enzyme (ACE) inhibitor-diuretic combination on serious vascular events in patients with diabetes, irrespective of initial blood pressure levels or the use of other blood pressure lowering drugs.

Methods The trial was done by 215 collaborating centres in 20 countries. After a 6-week active run-in period, 11 140 patients with type 2 diabetes were randomised to treatment with a fixed combination of perindopril and indapamide or matching placebo, in addition to current therapy. The primary endpoints were composites of major macrovascular and microvascular events, defined as death from cardiovascular disease, non-fatal stroke or non-fatal myocardial infarction, and new or worsening renal or diabetic eye disease, and analysis was by intention-to-treat. The macrovascular and microvascular composites were analysed jointly and separately. This trial is registered with ClinicalTrials.gov, number NCT00145925.

Findings After a mean of 4·3 years of follow-up, 73% of those assigned active treatment and 74% of those assigned control remained on randomised treatment. Compared with patients assigned placebo, those assigned active therapy had a mean reduction in systolic blood pressure of 5·6 mm Hg and diastolic blood pressure of 2·2 mm Hg. The relative risk of a major macrovascular or microvascular event was reduced by 9% (861 [15·5%] active *vs* 938 [16·8%] placebo; hazard ratio 0·91, 95% CI 0·83–1·00, p=0·04). The separate reductions in macrovascular and microvascular events were similar but were not independently significant (macrovascular 0·92; 0·81–1·04, p=0·16; microvascular 0·91; 0·80–1·04, p=0·16). The relative risk of death from cardiovascular disease was reduced by 18% (211 [3·8%] active *vs* 257 [4·6%] placebo; 0·82, 0·68–0·98, p=0·03) and death from any cause was reduced by 14% (408 [7·3%] active *vs* 471 [8·5%] placebo; 0·86, 0·75–0·98, p=0·03). There was no evidence that the effects of the study treatment differed by initial blood pressure level or concomitant use of other treatments at baseline.

Interpretation Routine administration of a fixed combination of perindopril and indapamide to patients with type 2 diabetes was well tolerated and reduced the risks of major vascular events, including death. Although the confidence limits were wide, the results suggest that over 5 years, one death due to any cause would be averted among every 79 patients assigned active therapy.

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Introduction

Prevention of the vascular complications of type 2 diabetes mellitus is a global health priority. By 2030, an estimated 350 million people will be living with diabetes worldwide.[1] Most people with this condition will die or be disabled as a consequence of vascular complications. In patients with diabetes and hypertension, all the main classes of antihypertensive drugs seem to reduce the risks of stroke and coronary heart disease.[2] Moreover, there is evidence that more intensive treatment, targeting lower blood pressure values, confers greater protection against these macrovascular outcomes.[3] Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers have also been shown to reduce the risk of development or progression of diabetic nephropathy.[4] Additionally, there is some evidence that more intensive therapy, targeting lower blood pressure values, confers greater protection against diabetic eye disease.[5]

These findings suggest that prevention strategies designed to increase the use of treatments for lowering blood pressure, and to improve levels of blood pressure control, could produce worthwhile reductions in the risks of macrovascular and microvascular complications of diabetes. Traditional strategies set arbitrary blood pressure levels at which treatment is initiated and arbitrary goals against which treatment should be titrated. This strategy neglects those diabetic patients without what is typically defined as hypertension, and yet for whom blood pressure remains an important determinant of their risk of vascular disease.[6] Additionally, this strategy is usually resource-intensive, needing multiple patient

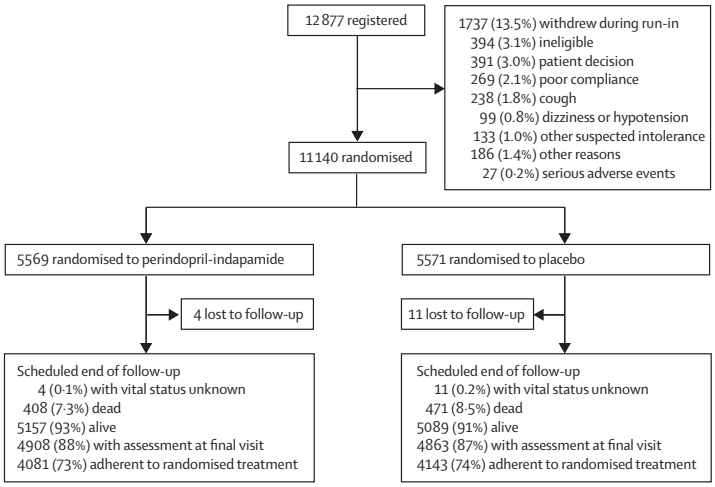

Figure 1: **Trial profile**

	Randomised treatment	
	Active (n=5569)	Placebo (n=5571)
Age (years), mean (SD)	66 (6)	66 (7)
Female, n (%)	2366 (43%)	2369 (43%)
Age when diabetes first diagnosed (years), mean (SD)	58 (9)	58 (9)
Previous vascular disease		
History of major macrovascular disease, n (%)	1798 (32%)	1792 (32%)
History of myocardial infarction, n (%)	678 (12%)	656 (12%)
History of stroke, n (%)	502 (9%)	520 (9%)
History of major microvascular disease, n (%)	568 (10%)	584 (10%)
History of macroalbuminuria†, n (%)	197 (4%)	204 (4%)
History of microvascular eye disease‡, n (%)	389 (7%)	404 (7%)
Blood pressure control		
Systolic blood pressure (mm Hg), mean (SD)	145 (22)	145 (21)
Diastolic blood pressure (mm Hg), mean (SD)	81 (11)	81 (11)
History of currently treated hypertension, n (%)	3802 (68%)	3853 (69%)
Other major risk factors		
Current smokers, n (%)	804 (14%)	878 (16%)
Serum total cholesterol (mmol/L), mean (SD)	5·2 (1·2)	5·2 (1·2)
Serum HDL cholesterol (mmol/L), mean (SD)	1·3 (0·3)	1·3 (0·4)
Urinary albumin:creatinine ratio (µg/mg), median (IQR)	15 (7 to 40)	15 (7 to 40)
Microalbuminuria, n (%)	1441 (26%)	1421 (26%)
Serum creatinine (µmol/L), mean (SD)	87 (23)	87 (26)
Serum haemoglobin A_{1c} concentration (%), mean (SD)	7·5 (1·6)	7·5 (1·6)
Body-mass index (kg/m²), mean (SD)	28 (5)	28 (5)

*Characteristics of participants recorded at the first (registration) visit, before active run-in. †Urinary albumin-creatinine ratio>300 µg/mg. ‡Proliferative diabetic retinopathy, retinal photocoagulation therapy, macular oedema, or blindness in one eye thought to be caused by diabetes.

Table 1: **Baseline* characteristics of randomised participants**

visits, careful monitoring of both blood pressure and side-effects, and the coordination of complex drug regimens. Perhaps partly as a consequence of such complexity, surveys of blood pressure control indicate that few patients receiving antihypertensive drugs achieve recommended goals for blood pressure.[7–10]

An alternative approach, to increase the use and effectiveness of treatment for lowering blood pressure in patients with diabetes, is to add a fixed-dose combination of blood pressure lowering drugs irrespective of initial blood pressure level or the use of other antihypertensive drugs.[11] This approach is more inclusive and less resource-intensive than the target-setting strategy. Although this approach might not produce the largest blood pressure reductions possible, it will shift the entire distribution of blood pressure values down in patients with diabetes, with minimum requirements for titration and, potentially, with fewer side-effects.[12]

The Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) trial was designed to assess the effects on vascular disease of such an approach using a fixed combination of the ACE inhibitor, perindopril, and the diuretic, indapamide, in a diverse population of patients with type 2 diabetes and a broad range of blood pressure values. Using a factorial design, the study will also assess the effects on the same outcomes of an intensive gliclazide MR-based glucose lowering regimen (aiming for a haemoglobin A_{1c} [HbA_{1c}] level of 6·5% or lower) compared with standard glucose control. Follow-up in the glucose arm of the study will be completed in December, 2007. Here we report the principal results from the blood pressure lowering arm of the study, completed in June, 2007.

Methods

ADVANCE is a randomised controlled trial done by 215 collaborating centres in 20 countries from Asia, Australasia, Europe, and North America. Approval for the trial was obtained from the institutional ethics committee of each centre and all participants provided written informed consent. Detailed study methods are published elsewhere[13] and are described here in brief. This trial is registered with ClinicalTrials.gov, number NCT00145925.

Participants

Patients were potentially eligible if they had been diagnosed with type 2 diabetes mellitus at the age of 30 years or older and were aged 55 years or older at entry to the study. Potentially eligible patients also needed to have at least one of the following: a history of major cardiovascular disease (stroke, myocardial infarction, hospital admission for transient ischaemic attack, hospital admission for unstable angina, coronary revascularisation, peripheral revascularisation, or amputation secondary to vascular disease), or at least one other risk factor for cardiovascular disease. Such risk factors were defined by the presence of at least one of the following: a history of major microvascular disease (macroalbuminuria [urinary albumin-creatinine ratio

>300 µg/mg], proliferative diabetic retinopathy, retinal photocoagulation therapy, macular oedema, or blindness in one eye thought to be caused by diabetes), current cigarette smoking, total cholesterol more than 6·0 mmol/L, HDL cholesterol less than 1·0 mmol/L, microalbuminuria (urinary albumin-creatinine ratio 30–300 µg/mg), diagnosis of type 2 diabetes mellitus made 10 years or more before entry, or age 65 years or older at entry. Patients with an indication for an ACE inhibitor were eligible for inclusion, unless they had a specific indication for an ACE inhibitor other than perindopril at a maximum dose of 4 mg a day. There were no blood pressure criteria for inclusion.

Patients were ineligible if, in the opinion of the investigator, they met any of the following exclusion criteria: a definite indication for, or contraindication to, any of the study treatments or the HbA_{1c} target (≤6·5%); a definite indication for long-term insulin therapy at study entry; or current participation in another clinical trial.

Procedures

Potentially eligible participants entered a 6-week pre-randomisation run-in period during which they received a fixed combination tablet consisting of perindopril (2 mg) and indapamide (0·625 mg). All other treatments were continued at the discretion of the responsible physician, with the exception of ACE-inhibitors; participants taking an ACE-inhibitor other than perindopril had this treatment withdrawn and were offered substitution with open-label perindopril at a dose of 2 mg or 4 mg a day. Those who adhered to, and tolerated, the run-in study drugs were randomly assigned, in a double-blind fashion, to combined perindopril (2 mg) and indapamide (0·625 mg) or matching placebo. After 3 months, the doses of randomised therapy were doubled to 4 mg for perindopril and 1·25 mg for indapamide, or matching placebo. Study treatments were allocated using a central, computer-based, randomisation service accessible by internet, telephone, and facsimile. Randomisation was stratified by study centre, history of macrovascular disease, history of microvascular disease, and background use of perindopril at baseline. The use of concomitant treatments during follow-up, including blood pressure lowering therapy, remained at the discretion of the responsible physician with two exceptions—the use of thiazide diuretics was not allowed, and open-label perindopril, to a maximum of 4 mg a day, was the only ACE-inhibitor allowed, thus ensuring that the maximum recommended dose of 8 mg for perindopril could not be exceeded by patients randomly assigned to active treatment. However, if at any time another ACE inhibitor or a thiazide diuretic was thought to be definitely indicated, study treatment could be withdrawn and alternate open-label treatment provided.

Participants were seen 3, 4, and 6 months after randomisation, and subsequently, every 6 months. At study

	Registration visit		End of follow-up	
	Active	Placebo	Active	Placebo
Blood pressure lowering drugs				
Perindopril, n (%)	490 (9%)†	449 (8%)†	2128 (45%)	2591 (55%)
Other ACE-I, n (%)	1914 (34%)	1969 (35%)	232 (5%)	213 (5%)
ARB, n (%)	289 (5%)	320 (6%)	453 (10%)	618 (13%)
β blockers, n (%)	1344 (24%)	1385 (25%)	1492 (31%)	1671 (35%)
Calcium antagonists, n (%)	1669 (30%)	1758 (32%)	1531 (32%)	2040 (43%)
Thiazides, n (%)	786 (14%)	808 (15%)	158 (3%)	217 (5%)
Other diuretics, n (%)	596 (11%)	577 (10%)	673 (14%)	749 (16%)
Other BP lowering drug, n (%)	700 (13%)	683 (12%)	463 (10%)	638 (14%)
Any BP lowering drug, n (%)	4166 (75%)	4200 (75%)	3634 (74%)	4024 (83)%
Other drugs				
Aspirin, n (%)	2445 (44%)	2449 (44%)	2680 (56%)	2574 (55%)
Other antiplatelets, n (%)	236 (4%)	269 (5%)	292 (6%)	269 (6%)
Statins, n (%)	1538 (28%)	1608 (29%)	2126 (44%)	2132 (45%)
Other lipid modifying drugs, n (%)	472 (9%)	464 (8%)	394 (8%)	309 (7%)
Gliclazide-MR, n (%)	433 (8%)‡	432 (8%)‡	2228 (47%)	2189 (46%)
Other sulphonylurea, n (%)	3570 (64%)	3520 (63%)	1467 (31%)	1491 (32%)
Metformin, n (%)	3399 (61%)	3352 (60%)	3321 (69%)	3390 (72%)
Any oral hypoglycaemic drug (%)	5082 (91%)	5047 (91%)	4438 (90%)	4422 (91%)
Insulin, n (%)	80 (1%)	79 (1%)	1581 (33%)	1431 (30%)

ACE-I=angiotensin converting enzyme inhibitor. ARB=angiotensin receptor blocker. BP=blood pressure. *Treatments at the first (registration) visit; participants entered the active run-in phase after this visit. †Percentage taking perindopril at the first (registration) visit; by the randomisation visit 47% were taking open-label perindopril in both groups. ‡Percentage taking gliclazide-MR at the first (registration) visit; by randomisation visit 49% were taking gliclazide-MR in both groups.

Table 2: **Concomitant treatments at baseline* and during follow-up**

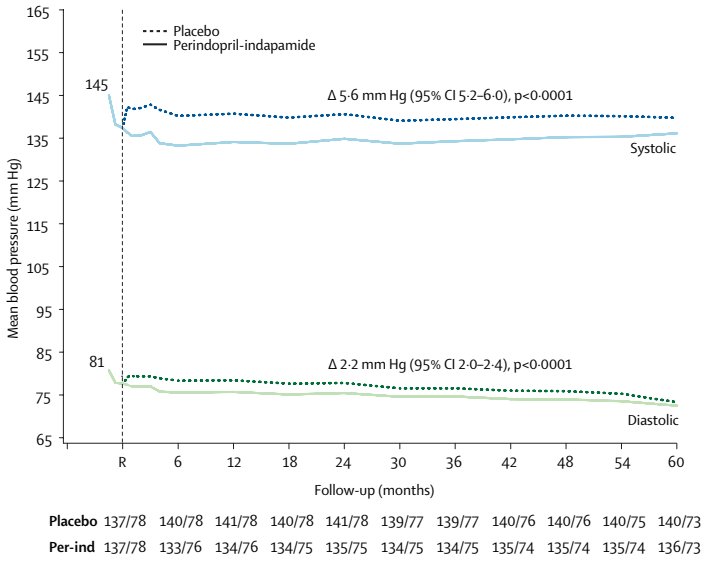

Figure 2: **Mean systolic and diastolic blood pressure during run-in on active treatment and after randomisation to active treatment or placebo**

Δ=average difference between randomised groups during follow-up. R=randomisation. Per-ind=perindopril-indapamide.

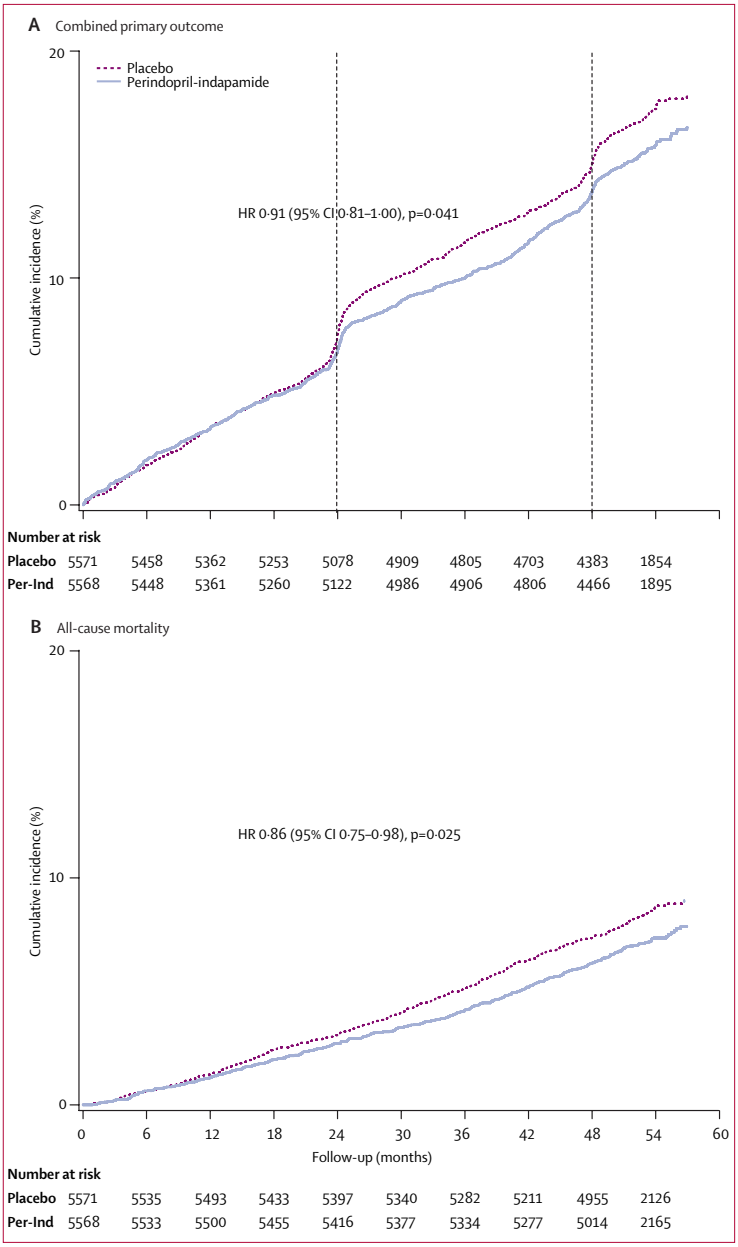

Figure 3: **For patients assigned active treatment or placebo, cumulative incidence of (A) combined major macrovascular or microvascular outcomes and (B) all-cause mortality**

Vertical broken lines indicate 24-month and 48-month study visits, at which additional information on microvascular events (measurement of urinary albumin-creatinine ratio and retinal examination) was obtained. For outcomes relating to these measurements, event times were recorded as the visit date. The curves were truncated at Month 57, by which time 99% of events had occurred. The effects of treatment (hazard ratios and p-values) were estimated from unadjusted Cox proportional hazard models that used all available data.

visits, information on adherence to, and tolerability of, study treatments, blood pressure, blood glucose, HbA_{1c}, lipid levels, and occurrence of study outcomes was obtained. Blood pressure was recorded as the mean of two measurements made after the patient was rested for at least 5 min in the seated position, using a standardised automated sphygmomanometer (Omron HEM-705CP, Tokyo, Japan). Additional information was obtained at the 2-year and 4-year follow-up visits, and included the urinary albumin-creatinine ratio, a formal retinal examination, a mini mental state examination, and a quality of life assessment.

The primary study outcomes were composites of major macrovascular and microvascular events. Major macrovascular events were cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. Major microvascular events were new or worsening nephropathy [development of macroalbuminuria, doubling of serum creatinine to a level of at least 200 µmol/L, need for renal replacement therapy, or death due to renal disease] or retinopathy [development of proliferative retinopathy, macular oedema, or diabetes-related blindness, or retinal photocoagulation therapy]).

The secondary outcomes included all-cause mortality, cardiovascular death, major coronary events (death due to coronary heart disease [including sudden death] and non-fatal myocardial infarction), total coronary events (major coronary events, silent myocardial infarction, coronary revascularisation, or hospital admission for unstable angina), major cerebrovascular events (death due to cerebrovascular disease or non-fatal stroke), and total cerebrovascular events (major cerebrovascular events, transient ischaemic attack, or subarachnoid haemorrhage). Other secondary outcomes were heart failure (death due to heart failure, hospitalisation due to heart failure, or worsening New York Heart Association class), peripheral vascular disease, new or worsening nephropathy, new or worsening retinopathy, development of microalbuminuria, visual deterioration, new or worsening neuropathy, cognitive function, dementia, and hospitalisations. Results for all pre-specified outcomes are reported.

An Endpoint Adjudication Committee, masked to treatment allocation, reviewed source documentation for all individuals who had a suspected primary endpoint or who died during follow-up. Outcomes were coded according to the 10th revision of the International Classification of Diseases. An independent Data and Safety Monitoring Committee reviewed unblinded data at yearly intervals throughout follow-up. This committee was charged with informing the study investigators if, at any time, there emerged evidence, beyond reasonable doubt, of a difference between randomised groups in survival or evidence that was likely to materially alter the management of patients with diabetes.

Statistical analysis

ADVANCE was originally designed to provide at least 90% power to detect a 16% or greater reduction in the relative risks of both major macrovascular events and major microvascular events using a 5% two-tailed test

with equal numbers allocated to active blood pressure treatment and placebo. Half-way through follow-up, the overall event rates (in active and placebo groups combined) were lower than expected. To enhance the statistical power of the trial to detect plausible treatment effects, two amendments dated Nov 30, 2005, were made to the study protocol: first, analyses of the primary outcomes were extended to include consideration of major macrovascular and microvascular events jointly as well as separately; and second, treatment and follow-up in the blood pressure arm was extended by 12 months.

Thus, the protocol pre-specified that the composite of major mascrovascular and microvasular outcomes would be included in the analyses of the primary outcomes. All analyses would also be by intention to treat. The effects of treatment on the primary and secondary endpoints were estimated from unadjusted Cox proportional hazard models. For participants with more than one outcome event during follow-up, survival time to the first relevant endpoint was used in each analysis. Participants were censored at their date of death or, for those still alive at the end of follow-up, the date of their last visit. Patients with an unknown vital status were censored when they were last known to be alive. Relative risk reductions are described in the text and figures as percentage reductions ([1–hazard ratio]×100). Differences between randomised groups during follow-up, in blood pressure and other continuous variables, were estimated from linear mixed models. Numbers needed to treat were calculated as reciprocals of the absolute risk differences with their normally-approximated 95% CIs.[14] All p values were calculated from two-tailed tests of statistical significance with a Type I error rate of 5%. As is common practice in the analysis of data from large scale trials in which all major outcomes are reported (many of which are correlated), no adjustment for multiple statistical testing was done.[15]

Separate estimates for treatment effects were obtained among subgroups of participants defined by age, sex, history of vascular disease, ancillary treatments, blood pressure, and HbA_{1c} at study entry. No subgroup analyses were pre-specified. Homogeneity of treatment effects for both categorical and continuous variables was tested by adding interaction terms to the relevant Cox models. All analyses were done using SAS version 9.1.

Role of the funding source

ADVANCE was funded by grants from Servier and the National Health and Medical Research Council of Australia. The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study. The Management Committee had final responsibility for the decision to submit for publication.

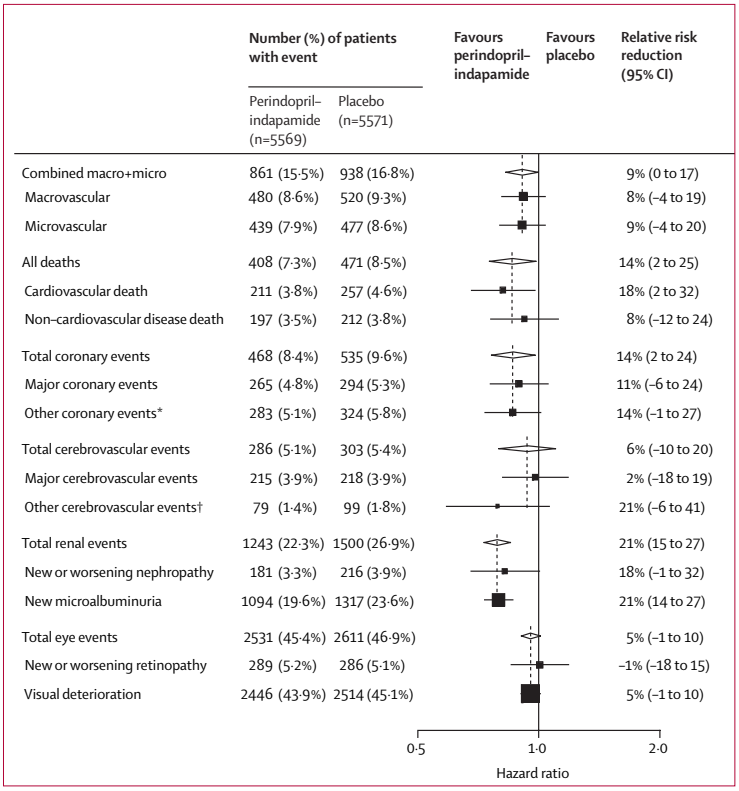

Figure 4: **Effects of study treatment on deaths, coronary events, cerebrovascular events, renal events, and eye events**

*Other coronary events=unstable angina requiring hospitalisation, coronary revascularisation or silent myocardial infarction. †Other cerebrovascular events=transient ischaemic attack (including amaurosis fugax) or subarachnoid haemorrhage. Black squares=point estimates (with area proportional to number of events); horizontal lines=95% CI. Diamonds=point estimate and 95% CI for overall effects. Vertical broken lines=point estimates for overall effect, within categories.

Results

12 877 potentially eligible participants were registered, 1737 (13·5%) were subsequently withdrawn during the 6-week active run-in period, and 11 140 (86·5%) were randomised (figure 1). As would be expected in a population of this size, there was good balance between randomised groups across a range of characteristics at entry (tables 1 and 2). Around a third of patients had a history of major macrovascular disease and about 10% had a history of major microvascular disease at baseline (table 1). The mean entry blood pressure of randomised patients was 145/81 mm Hg and 41% had a blood pressure less than 140 mm Hg systolic and 90 mm Hg diastolic. At randomisation, 47% of patients were receiving treatment with open-label perindopril (2–4 mg a day). Additionally, 47% of patients were receiving anti-platelet therapy, 35% were receiving cholesterol lowering drugs, and 91% were receiving oral hypoglycaemic agents at baseline (table 2).

The mean duration of follow-up was 4·3 years (24 005 patient-years in the active treatment group and

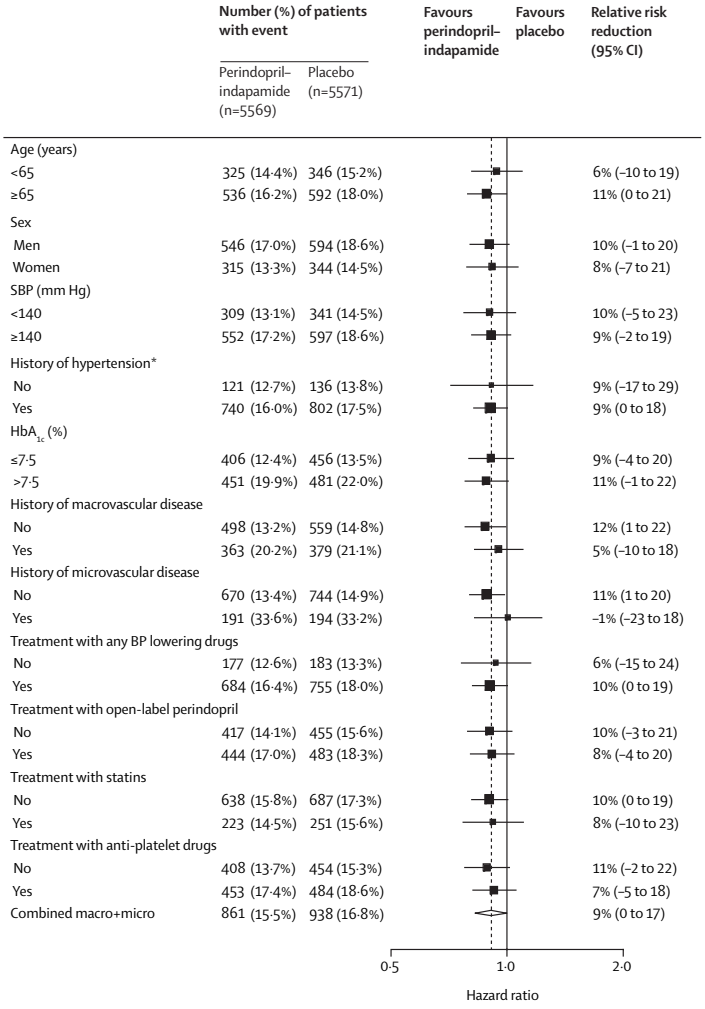

Figure 5: **Effects of study treatment on combined major macrovascular or microvascular events in subgroups of participants defined by characteristics at baseline**

*History of hypertension=blood pressure lowering drugs used at baseline, or systolic pressure >140 mm Hg or diastolic blood pressure >90 mm Hg at study entry. Vertical broken line=point estimate for overall effect.

23 845 patient-years in the placebo group) and the range was from less than 1 month to 5·6 years. During follow-up, randomised treatment was continued for 20 001 patient-years (83%) in the active treatment group and 20 849 patient-years (87%) in the placebo group. At the end of follow-up, 4081 (73%) patients in the active treatment group and 4143 (74%) patients in the placebo group were adherent to randomised therapy. The main reasons for permanent discontinuation were participant decision or inability to attend clinic visits (active 521 [9·4%], placebo 635 [11·4%]), cough (active 184 [3·3%], placebo 72 [1·3%]) and hypotension or dizziness (active 69 [1·2%], placebo 22 [0·4%]), and serious adverse events (active 67 [1·2%], placebo 66 [1·2%]). Serious suspected adverse drug reactions were reported in 47 (0·8%) patients randomised to active treatment and 31 (0·6%) patients allocated placebo, including five cases of angioedema (three active, two placebo), none of which was fatal.

Over the duration of follow-up, blood pressure was reduced by an average of 5·6 (SE 0·2) mm Hg systolic and 2·2 (SE 0·1) mm Hg diastolic in patients assigned active treatment compared with those assigned placebo (figure 2).

At the end of follow-up, mean levels of HbA_{1c} (6·9%), fasting plasma glucose (7·2 mmol/L), total cholesterol (5·0 mmol/L) and HDL cholesterol (1·0 mmol/L) were not different between randomised groups (all p>0·1). Fewer participants randomised to active treatment were taking other blood pressure lowering therapy (including background perindopril) at the final visit, compared with those allocated placebo (74% *vs* 83%) but use of lipid modifying therapy, antiplatelet medication, and glucose lowering treatments (including insulin) was similar (table 2). The large increase in insulin use during follow-up in both treatment groups mainly indicates the intensified glucose lowering regimen being studied in the other factorial arm of the trial.

1799 participants had a major macrovascular or a major microvascular event during follow-up: 861 (15·5%) in the active treatment group and 938 (16·8%) in the placebo group (relative risk reduction 9% [95% CI 0–17%; p=0·041]; figure 3). On this basis, we estimated that one participant in every 66 (95% CI 34–1068) assigned active treatment would avoid at least one major macrovascular or microvascular event over 5 years. The proportional effects of active treatment on major macrovascular outcomes (relative risk reduction 8% [95% CI –4 to 19%; p=0·16]) and major microvascular outcomes (9% [–4 to 20%; p=0·16]) were similar, though not separately significant.

Data for vital status at the end of follow-up were missing for only 15 randomised participants (figure 1). During the study 879 participants died: 408 (7·3%) in the active treatment group and 471 (8·5%) in the placebo group (relative risk reduction 14% [95% CI 2–25], p=0·025; figure 3). Over 5 years, one death in every 79 (95% CI 43 to 483) patients assigned active treatment was estimated to have been averted. This reduction in total mortality was mainly due to a reduction in cardiovascular deaths (3·8% *vs* 4·6%; relative risk reduction 18% [95% CI 2 to 32%], p=0·027) in participants assigned active treatment, with no significant difference between randomised groups in non-cardiovascular deaths (3·5% *vs* 3·8%; 8% [–12 to 24%], p=0·41).

Significantly fewer total coronary events occurred in participants randomly assigned to active treatment compared with those assigned placebo (8·4% *vs* 9·6%; 14% [2–24%], p=0·020; figure 4). Over 5 years, one patient in every 75 (95% CI 41–453) assigned active treatment would have avoided at least one coronary event. There

was no significant difference between randomised groups in either total cerebrovascular events (relative risk reduction 6% [95% CI –10 to 20%], p=0·42) or heart failure (2% [–20 to 19%], p=0·86).

Active treatment was associated with a significant 21% reduction in all renal events (95% CI 15–27%, p<0·0001), with a borderline significant reduction in new or worsening nephropathy (3·3% *vs* 3·9%; relative risk reduction 18% [–1 to 32%], p=0·055) and a significant reduction in the development of microalbuminuria (19·6% *vs* 23·6%; 21% [14–27%]; p<0·0001). Over 5 years, one patient in every 20 (95% CI 15–30) assigned active treatment would have avoided one renal event (mostly the onset of new microalbuminuria). There was no significant difference between randomised groups in the rate of new or worsening retinopathy (relative risk reduction –1% [–18 to 15%], p=0·94), including the need for retinal photocoagulation (–14% [–41 to 8%], p=0·23).

There was also no significant effect of active treatment on any of the other secondary outcomes of visual deterioration (relative risk reduction 5% [95% CI –1 to 10%]; p=0·10), new or worsening neuropathy (1% [–5 to 7%]; p=0·68), cognitive function (2% [–9 to 12%], p=0·72), dementia (–4% [–64% to 33%], p=0·85), and total hospitalisations (–3% [–9% to 3%], p=0·39).

The effects of study treatment on the combined major macrovascular and microvascular outcome were broadly consistent across a range of participant subgroups defined by baseline characteristics (p for heterogeneity all >0·1; figure 5). Additionally, there was no evidence of an interaction between the effect of treatment and baseline systolic blood pressure considered as a continuous variable (p>0·5). Similarly, there was no evidence of heterogeneity of treatment effects between the same subgroups for other outcomes including total mortality, cardiovascular death, total coronary events, total cerebrovascular events, and microalbuminuria (data not shown).

Discussion

In ADVANCE, the routine administration of a fixed combination of perindopril and indapamide to a broad range of patients with type 2 diabetes reduced the risk of death and the risk of major macrovascular or microvascular events. The separate reductions in macrovascular and microvascular events were similar but were not independently significant. There were significant reductions in total coronary and renal events, but not in total cerebrovascular or diabetic eye events. The benefits were achieved against a background of medical care that, by the end of follow-up, included non-study drugs for lowering blood pressure for more than three-quarters of participants, and one or more glucose lowering agents for more than 90%, including insulin for a third of patients. The effects of the study drugs seemed to be independent of the use of ancillary treatments at baseline, including ACE inhibitors, which were provided to about half the study participants. There was no evidence that the effects of study drugs were dependent on initial blood pressure, HbA_{1c}, age, sex, or vascular disease history.

Over an average of 4·3 years of follow-up, the risk of a major macrovascular or microvascular event was reduced from 16·8% to 15·5%, suggesting that for every 66 patients commencing long-term treatment with perindopril and indapamide, one patient would avoid at least one major vascular event in 5 years as a direct consequence of study treatment. The major contributor to the 9% overall reduction in the risk of major macrovascular or microvascular events was an 18% reduction in the risk of death from cardiovascular disease, which largely accounted for the 14% reduction in total mortality. Although effects of blood pressure lowering agents on total mortality have rarely been seen in individual trials in patients with hypertension[16] or diabetes,[17] meta-analyses have previously confirmed that drugs for lowering blood pressure can improve survival.[3,18] From the results of ADVANCE, it seemed that over 5 years, one death would be averted in every 79 patients commencing treatment with the study drugs.

ADVANCE was initially designed to detect reductions of about 16% in the relative risk of each of the major macrovascular and microvascular outcomes, assuming yearly event rate of 3% in the placebo group for each. However, the actual event rate for the two outcomes combined was only 4% per year, which is much lower than the event rates seen in previous large trials of blood pressure lowering regimens in type 2 diabetes.[17,19] Although the results suggest that the effects of treatment are probably smaller than initially anticipated, the upper confidence limits remain consistent with true effects of this size, for both the combined and individual primary outcomes. No adjustments were made for multiple statistical testing,[15] but the results for the primary study outcomes seem to be both internally and externally consistent. The estimates for treatment effect were mostly in the same direction for other events not included in the primary outcomes (figure 4) and for the combined primary outcome, were similar in multiple subgroups defined by characteristics at baseline (figure 5).

Additionally, treatment effects on coronary events, cardiovascular death, and total mortality in ADVANCE were broadly consistent with effects seen in earlier meta-analyses of placebo-controlled trials of ACE-inhibitor-based regimens in populations including individuals with and without diabetes.[3,20,21] Although there was no significant effect of study treatment on cerebrovascular events, the CIs for the treatment effect in ADVANCE overlap with those described in the meta-analyses. Given that previous epidemiological and clinical trial evidence does not predict heterogeneity between diabetic and non-diabetic subgroups in the relative effects of blood pressure lowering on stroke,[2,6] ADVANCE results are not likely to indicate any real

differences in the treatment response of those with and without diabetes. The greater use of calcium channel blockers in the placebo group (43% at the end of follow-up) than the active treatment group (32% at the end of follow-up) might be relevant, but the play of chance remains the most likely explanation for the absence of any clear effect of study treatment on cerebrovascular outcomes.

Study treatment in ADVANCE produced a one-fifth reduction in the development of microalbuminuria. This result is consistent with other data indicating that ACE inhibitors, compared with placebo or calcium antagonists, are effective in preventing the development of microalbuminuria.[4] Treatment with ACE inhibitors has also been shown to be effective in reducing progression to macroalbuminuria,[4] and the reduction in the incidence of new or worsening nephropathy in ADVANCE, albeit of borderline statistical significance, is entirely consistent with these data. Such effects of treatment are important in view of the high risk of progression to end stage renal failure and premature death in patients who develop diabetic nephropathy, as well as the emerging evidence of substantial cardiovascular risks associated with progression of renal impairment.[22,23]

There was no evidence that active treatment in ADVANCE reduced the incidence of new or worsening microvascular eye disease, including that defined by retinal photocoagulation. This finding contrasts with those of the United Kingdom Prospective Diabetes Study (UKPDS),[5] in which there was a one-third reduction in microvascular eye disease (largely the result of a reduction in retinal photocoagulation) in patients randomised to more intensive antihypertensive therapy. However, the ADVANCE results are consistent with the findings of the Heart Outcomes Prevention Evaluation (HOPE) study in the subgroup of participants with diabetes,[17] among whom there was no significant reduction in the use of laser photocoagulation after treatment with ramipril. The use of laser photocoagulation is a specific, but insensitive, marker for progression of retinal microvascular disease that is undoubtedly affected by variation in treatment practice and health care access. In ADVANCE, the use of laser photocoagulation was much less frequent (0·6% per year for those assigned placebo) than in previous studies (1·7% per year in UKPDS and 2·2% per year in HOPE). The low rate of laser photocoagulation in ADVANCE limited the power of the study to detect plausibly moderate effects of study treatment on this outcome. Further data for the potential effects of study treatment on retinopathy will be available from analyses of retinal photographs obtained in a subgroup of participants in ADVANCE.[24]

The fixed combination regimen used in ADVANCE was well tolerated. During the pre-randomisation run-in period, in which all potentially eligible patients received active treatment, only 3·6% were withdrawn because of suspected side-effects. After an average of 4·3 years of follow-up post-randomisation, adherence to active treatment was 73%, only 1% less than adherence to placebo. This finding indicates that a short course of active treatment identifies the small proportion of patients who are intolerant. Among all others, treatment can be continued long-term, with adherence comparable to that seen with placebo. This result has important practical implications for health services delivery, since only one follow-up visit is needed to establish a patient's suitability for long-term treatment with this regimen. Thereafter, follow-up visits can be maintained at 3–6-month intervals with minimum requirement for titration. This simple strategy, with its attendant reductions in vascular events and death, should prove practical and affordable in most clinical circumstances, and might have special relevance in those primary health care settings where there are practical barriers to providing individually titrated treatment regimens for patients with diabetes.

The consistency of the relative effects across subgroups indicate that the absolute benefits conferred by treatment will be established mainly by each patient's future risk of vascular complications, rather than their initial level of blood pressure alone. These results support the provision of treatment, not on the basis of arbitrary cutoffs for blood pressure, but rather on assessment of vascular risk, which is raised in patients with type 2 diabetes, even in the absence of hypertension. However, a 9% reduction in combined macrovascular and microvascular events, including an 18% reduction in cardiovascular deaths, represents only partial reversal of the doubling of fatal and non-fatal vascular risks typically conferred by diabetes in both Asian and white populations.[25,26] Further reductions in blood pressure might confer even larger reductions in risk.[3] Considering that less than half of all participants in ADVANCE were treated with a statin, an increase in the use of these agents would be expected to produce substantial additional reductions in macrovascular events.[27,28] Additionally, greater use of antiplatelet drugs might further reduce these risks, although for the primary prevention of vascular events in patients with diabetes, this reduction remains to be proven in randomised trials.[29] Reduction of blood glucose levels with regimens based on sulphonylureas or insulin have been shown to reduce microvascular eye complications, but there remains uncertainty about the effects of such treatment on microvascular renal complications, as well as macrovascular complications of diabetes.[19,30] Follow-up in the glucose lowering arm of ADVANCE will end in December, 2007, and the results will provide further evidence about the effects of intensive glucose control on these and other outcomes.

In summary, the results of ADVANCE indicate that the routine administration of a fixed combination of perindopril and indapamide to a broad range of patients with diabetes reduces the risks of death and major macrovascular or microvascular complications, irre-

spective of initial blood pressure level or ancillary treatment with the many other preventive treatments typically provided to diabetic patients today. The study treatment was well tolerated, needed little monitoring or titration and is, therefore, suitable for use in a wide range of clinical circumstances worldwide. If the benefits seen in ADVANCE were applied to just half the population with diabetes worldwide, more than a million deaths would be avoided over 5 years. For these reasons, there is now a case for considering such treatment routinely for patients with type 2 diabetes.

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Importance of Blood Pressure Lowering in Type 2 Diabetes: Focus on ADVANCE

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Abstract: Routine blood pressure lowering with the fixed combination of perindopril and indapamide in 11,140 patients with type 2 diabetes was very well tolerated and produced substantial benefits in reducing all-cause and cardiovascular mortality, the primary combined outcome of macro- or microvascular events, total coronary events, and total renal events, as reported previously. We present here a wealth of evidence, most of it previously published either in journal articles or in recent abstract form, that the relative risk reductions conferred by the combination of perindopril and indapamide are broadly consistent across subgroups defined by a wide range of baseline characteristics, including blood pressure at entry, age from below 65 to above 75 years, total cardiovascular risk defined according to the European guidelines, stage of chronic disease, and cognitive function. Furthermore, we report that the absolute risk reductions are significantly greater in those with increased cardiovascular risk, with more advanced nephropathy and in older subjects. We confirm that the effects of blood pressure lowering with perindopril–indapamide and of intensive glucose control with the gliclazide modified release (MR)–based regimen are independent and produce substantial additional benefits when combined. We also discuss these results in the context of other major trials and demonstrate how they extend the evidence on the benefits of blood pressure lowering in patients with diabetes. Finally, we present evidence that the results of The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE trial) are broadly generalizable to patients with type 2 diabetes in community practice, and that if the joint benefits from routine blood pressure lowering with perindopril–indapamide and more intensive control with the gliclazide-MR–based regimen were applied worldwide, close to 2 million lives would be saved over the next 5 years.

Key Words: perindopril, indapamide, type 2 diabetes, blood pressure lowering

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INTRODUCTION

The prevention of vascular and renal complications of type 2 diabetes constitutes a major challenge and a global health priority. The prevalence of diabetes is increasing at an alarming pace in both developed and developing countries and it is predicted that by 2030, around 350 million people will have diabetes worldwide.[1] The most common cause of death in patients with type 2 diabetes is coronary heart disease with renal disease, stroke, and heart failure making substantial contributions.[2] This increase in the risk of vascular disease in people with diabetes is at least in part accounted for by the raised levels of other risk factors such as blood pressure and lipids. Indeed, hypertension and diabetes are often termed "the bad companions" due to their frequent association and the large increase in the burden of cardiovascular and renal disease observed when they coexist.

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation trial (ADVANCE) was initiated in the year 2000 to address the burden of vascular and renal disease associated with blood pressure in patients with type 2 diabetes. ADVANCE was planned to test the hypothesis that blood pressure lowering would reduce this burden not only in hypertensive patients with diabetes but also in normotensive patients with type 2 diabetes. Although there was strong evidence from observational studies, to link blood pressure with vascular disease in diabetes,[3] at the time the ADVANCE was conceived, clinical trial evidence of the benefits of blood pressure lowering in diabetes was limited to hypertensive patients.[4,5] ADVANCE was designed to fill the gap in our knowledge and to demonstrate that the benefits of blood pressure lowering were similar in patients with type 2 diabetes whether hypertensive or not.[6,7] ADVANCE was also planned as a factorial study, with a second arm examining the potential reduction in the burden of vascular and renal disease in diabetic patients treated with a gliclazide modified release (MR)–based intensive glucose control regimen.[6,7] Thus, the factorial trial design provided an opportunity to examine in the same trial population, whether any reductions in vascular disease, in renal disease, or in mortality, observed in the 2 arms were independent and additive.[6,7]

In this article, we give a brief summary of the main results, previously published, of blood pressure lowering with

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the fixed combination of perindopril and indapamide, both alone and jointly with gliclazide-MR–based intensive glucose control.[8,9] We then describe in greater detail the effects of blood pressure lowering in a variety of important subgroups, demonstrating the remarkable consistency and generalizability of the benefits obtained with the fixed combination of perindopril and indapamide.

SUMMARY OF MAIN RESULTS OF BLOOD PRESSURE LOWERING WITH PERINDOPRIL-INDAPAMIDE IN ADVANCE

All participants were randomized to receive either active treatment with the fixed combination of perindopril and indapamide (2.0 mg/0.625 mg for the first 3 months, then 4.0 mg/1.25 mg thereafter) or matching placebo. The baseline characteristics of the ADVANCE population have been fully described elsewhere.[8,9] Mean baseline blood pressure among 11,140 randomized patients with type 2 diabetes was 145/81 mm Hg, with 41% having a blood pressure below 140/90 mm Hg and 20% below 130/90 mm Hg.[8] The mean blood pressure was reduced by an average of 5.6/2.2 mm Hg more in the group receiving perindopril–indapamide than in that on placebo, over the average 4.3-year period of follow-up.[8] The average blood pressure achieved during randomized treatment was 134.7/74.8 and 140.3/77.0 mm Hg in those on active treatment and placebo, respectively. The primary outcomes were composites of macrovascular events (nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death) and microvascular events (new or worsening nephropathy or retinopathy).[8,9]

Blood pressure lowering with the fixed combination of perindopril and indapamide resulted in substantial reductions in mortality, in vascular events, and in renal disease in particular, as shown in Figure 1.[8] These were reductions of 14% and 18% in all cause and cardiovascular mortality, respectively, with a 9% reduction in the combined primary outcome of macrovascular or microvascular events. There were also significant reductions of 14% in total coronary heart disease events and 21% in total renal events (Fig. 1).[8]

As reported previously, the magnitude of the reduction in the primary combined outcome was consistent across a broad range of subgroups defined by baseline characteristics including age, sex, systolic blood pressure, treatment with any blood pressure lowering drug, treatment with statins, or treatment with antiplatelet agent.[8]

Finally, the fixed combination of perindopril–indapamide was particularly well tolerated, with almost no loss to follow-up and with adherence to randomized therapy virtually the same as for placebo.[8]

EFFECTS OF LOWERING BLOOD PRESSURE ON MAJOR CLINICAL OUTCOMES ACCORDING TO BASELINE BLOOD PRESSURE

As reported in the main results article, blood pressure lowering with perindopril and indapamide significantly reduced the combined primary outcome by 9% overall.[8] The reductions in this primary combined outcome were also 9% in those with a history of hypertension or a baseline blood pressure >140/90 mm Hg, and 9% in those without a history of hypertension and a blood pressure <140/90 mm Hg, though these results were not separately significant.

More recent analyses have examined the effects of blood pressure lowering with perindopril–indapamide on a composite of total renal events comprising new onset micro- or macroalbuminuria, doubling of serum creatinine to >200 μmol/L, end stage renal disease, or renal death.[10] Active treatment reduced this composite renal outcome by 21% over the follow-up period of 4.3 years.[10] As shown in Table 1A, these effects were consistent across subgroups defined by baseline blood pressure, from levels below 120 mm Hg (systolic) or 70 mm Hg (diastolic) to levels about 160 mm Hg (systolic) and above 90 mm Hg (diastolic).[10] Furthermore, lower systolic blood pressure levels achieved during follow-up were associated with progressively lower rates of renal events, even down to levels below 110 mm Hg.[10] This simple treatment with perindopril–indapamide succeeded in preventing one renal event among every 20 patients with type 2 diabetes

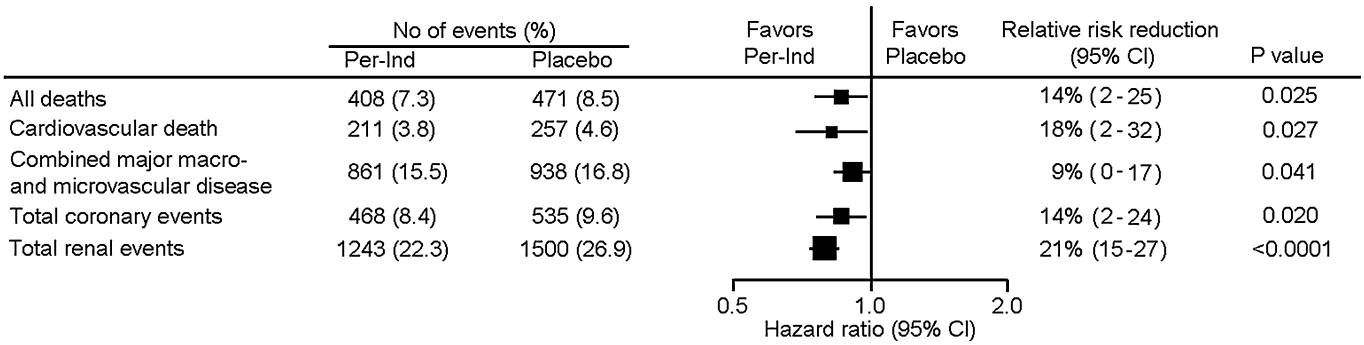

FIGURE 1. Effects of blood pressure lowering on deaths, macrovascular and microvascular disease. Total renal events represent a composite of new or worsening nephropathy and new microalbuminuria. Total coronary events represent a composite of nonfatal myocardial infarction, fatal coronary heart disease, and coronary revascularization. Solid boxes represent estimates of treatment effect: centers of the boxes are placed at the estimates of effect, the area of the boxes is proportional to the number of events, and horizontal lines represent the corresponding 95% confidence intervals. Per = perindopril, Ind = indapamide. Adapted from Ref. 8 with permission from Elsevier.

TABLE 1. Effects of Blood Pressure Lowering on Major Clinical Outcomes According to (A) Blood Pressure, (B) Chronic Kidney Disease Stage, and (C) Cognitive Function at Baseline

	No. of Events (%)		Relative Risk Reduction (95% CI)	*P* for Homogeneity
	Per–Ind	Placebo		
(A) Blood pressure				
Total renal events				
SBP <120 mm Hg	134 (21.8)	167 (29.8)	30% (12 to 44)	0.75
SBP 120–139 mm Hg	367 (21.1)	431 (24.0)	15% (3 to 26)	
SBP 140–159 mm Hg	439 (22.6)	563 (28.1)	25% (15 to 34)	
SBP ≥160 mm Hg	303 (23.8)	339 (27.9)	19% (5 to 30)	
Total renal events				
DBP <70 mm Hg	208 (24.6)	240 (27.2)	16% (−2 to 30)	0.85
DBP 70–79 mm Hg	387 (22.1)	481 (27.4)	23% (12 to 33)	
DBP 80–89 mm Hg	386 (20.7)	479 (26.1)	24% (13 to 34)	
DBP ≥90 mm Hg	262 (23.5)	300 (27.3)	19% (4 to 31)	
(B) CKD stage				
All deaths				
No CKD	155 (5.1)	170 (5.5)	9% (−13 to 27)	0.74
CKD stage 1 or 2	114 (9.2)	126 (10.1)	10% (−10 to 30)	
CKD stage ≥3	117 (11.6)	135 (13.2)	13% (−10 to 33)	
Cardiovascular death				
No CKD	72 (2.4)	72 (2.3)	0% (−39 to 28)	0.36
CKD stage 1 or 2	61 (4.9)	79 (6.4)	23% (−7 to 45)	
CKD stage ≥3	66 (6.5)	82 (8.0)	20% (−11 to 42)	
Major macrovascular events				
No CKD	202 (6.6)	197 (6.4)	−3% (−25 to 16)	0.27
CKD stage 1 or 2	128 (10.3)	142 (11.4)	11% (−13 to 30)	
CKD stage ≥3	126 (12.4)	143 (14.0)	13% (−10 to 32)	
(C) Cognitive function				
All deaths				
MMSE ≥28	277 (6.4)	324 (7.3)	16% (1 to 28)	0.32
MMSE 24–27	112 (10.2)	131 (11.5)	12% (−13 to 31)	
MMSE ≤23	18 (16.7)	16 (15.4)	−6% (−108 to 46)	
Cardiovascular death				
MMSE ≥28	140 (3.2)	171 (3.9)	19% (−1 to 36)	0.37
MMSE 24–27	62 (5.7)	72 (6.3)	11% (−25 to 37)	
MMSE ≤23	9 (8.3)	14 (13.5)	37% (−45 to 73)	
Major macrovascular events				
MMSE ≥28	338 (7.8)	364 (8.2)	8% (−6 to 21)	0.96
MMSE 24–27	123 (11.2)	138 (12.2)	9% (−16 to 28)	
MMSE ≤23	19 (17.6)	18 (17.3)	−3% (−96 to 46)	

Adapted partially from references 10 and 16 with permission from American Society of Nephrology and Springer, respectively.
Per = perindopril, Ind = indapamide, 95% CI = 95% confidence interval, SBP = systolic blood pressure, DBP = diastolic blood pressure, CKD = chronic kidney disease.

who were treated for 5 years, independent of baseline blood pressure or of blood pressure lowering treatment at entry.[10]

EFFECTS OF LOWERING BLOOD PRESSURE ON MAJOR CLINICAL OUTCOMES ACCORDING TO AGE AT BASELINE

The average age (standard deviation) of the 11,140 randomized patients in the ADVANCE trial was 66 (7) years at entry.[8] Blood pressure lowering treatment with perindopril–indapamide produced similar reductions in blood pressure in those above and below 65 and 75 years of age.[11] Statistical analysis confirmed there was no significant interaction between age and treatment effects for any of the major clinical outcomes. As can be seen in Figure 2, the reductions in relative risk of mortality and of major vascular outcomes were similar in participants above and below 65 years of age and above and below 75 years of age, though in many cases there was a tendency toward a greater reduction in the older age group.[11] Furthermore, the absolute benefits conferred were considerably greater in the older subjects, especially those over 75 years of age.

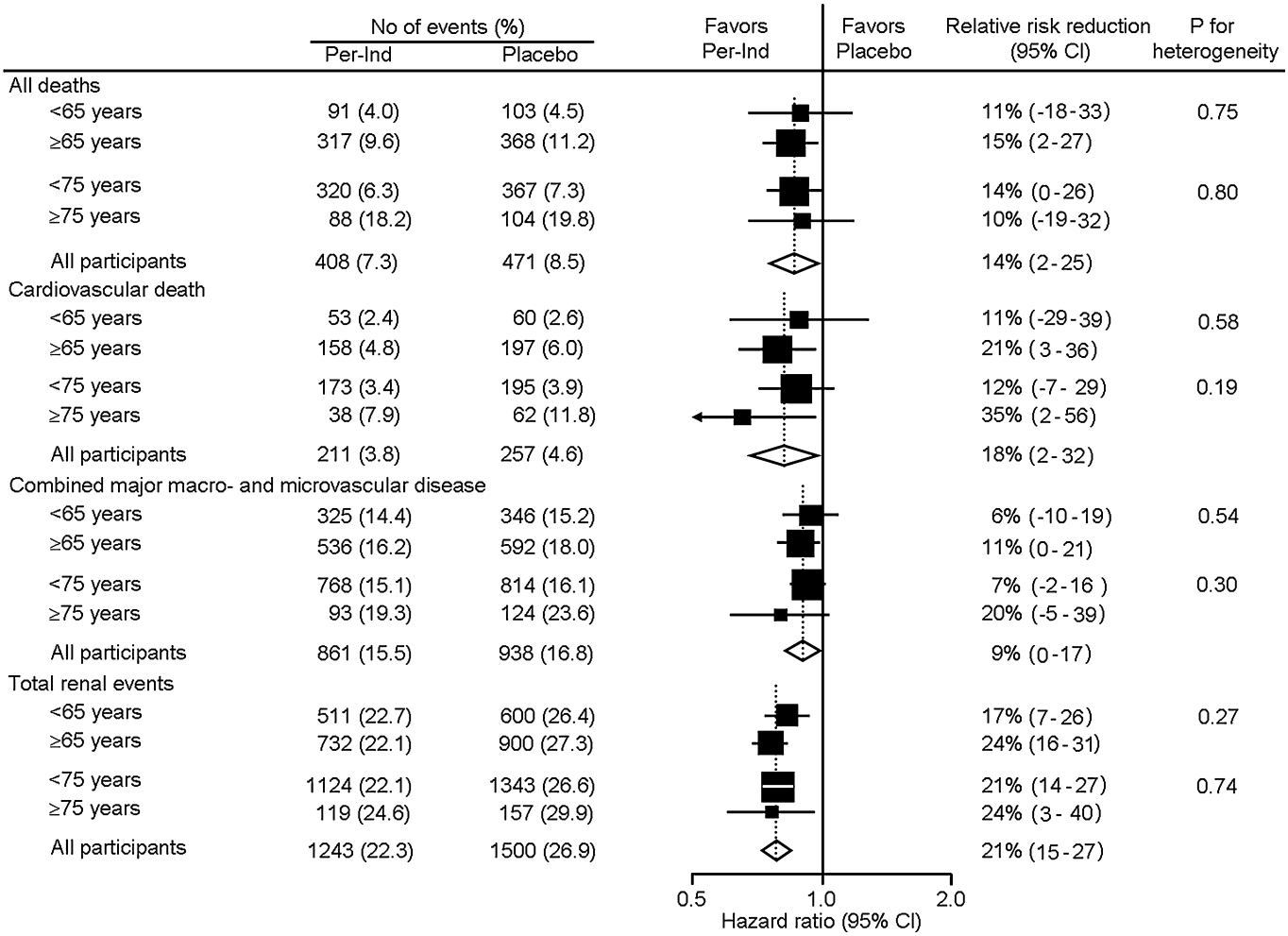

FIGURE 2. Effects of blood pressure lowering on major clinical outcomes in patients below and above 65 and 75 years of age. Solid boxes represent estimates of treatment effect in subgroups. The centers of the diamonds represent the point estimates and their widths represent the 95% confidence intervals for overall treatment effect. The vertical dotted line represents the point estimate for overall effect in all participants. Other conventions as for Figure 1.

EFFECTS OF LOWERING BLOOD PRESSURE ON MAJOR CLINICAL OUTCOMES ACCORDING TO BASELINE ALBUMINURIA AND RENAL FUNCTION

A recent report from ADVANCE has confirmed that albuminuria and impaired renal function, measured as the estimated glomerular filtration rate (eGFR) are separate and independent risk factors for cardiovascular and renal events in patients with type 2 diabetes.[12] Further, analyses have confirmed that as kidney disease progresses from absent, through stage 1 to stage 5,[13] and as albuminuria increases and eGFR decreases, the relative risk reduction resulting from treatment with the fixed combination of perindopril and indapamide remains broadly consistent, with no significant heterogeneity among subgroups characterized by these renal parameters at baseline.[14,15]

Thus, in patients with urinary albumin:creatinine ratio (UACR) above and below 30 mg/g, active treatment reduced blood pressure by similar amounts and resulted in comparable reductions in the relative risk of all-cause mortality, cardiovascular death, and major macrovascular events, with no heterogeneity in the magnitude of these treatment effect.[14] In much the same way, there was no heterogeneity in these outcomes among patients without kidney disease at baseline and those with various stages of kidney disease at entry to the study (Table 1B).[15] However, it should be noted that the absolute benefits of treatment almost doubled in those with UACR above 30 mg/g compared with those with UACR below 30 mg/g[14] and those with more advanced stages of kidney disease, where the number needed to treat to save one death from any cause was reduced to 50, compared with 103 for patients without evidence of kidney disease at baseline.[15]

EFFECTS OF LOWERING BLOOD PRESSURE ON MAJOR CLINICAL OUTCOMES ACCORDINGLY TO COGNITIVE FUNCTION AT BASELINE

Cognitive function was assessed using the Mini Mental State Examination (MMSE) at baseline, at 2 yearly intervals

during follow-up, and at the end of follow-up as fully described in a recent report.[16] Once again, active treatment with the fixed combination of perindopril and indapamide produced similar and sizeable risk reductions across subgroups defined by cognitive function at baseline, with cognition defined as normal for MMSE ≥ 28, as "mild dysfunction" for MMSE of 24–27, and as "severe dysfunction" for MMSE of 23 or less (Table 1C).[16] Thus, the benefits of lowering blood pressure with perindopril–indapamide are not only evident in the elderly, but also in those with impaired cognitive function. Interestingly, the risks of all-cause mortality, of cardiovascular death, and of major macrovascular events were greater in those with cognitive dysfunction at baseline than in those with normal cognitive at entry.[16]

EFFECTS OF LOWERING BLOOD PRESSURE ON MAJOR CLINICAL OUTCOMES ACCORDING TO BASELINE CARDIOVASCULAR RISK

Total absolute cardiovascular risk is increasingly recommended to guide the treatment of patients with vascular diseases, particularly those with type 2 diabetes. Accordingly, we assessed the effects of routine administration of the fixed combination of perindopril and indapamide to patients participating in ADVANCE,[17] according to baseline cardiovascular risk as defined in the 2007 European Society of Hypertension/European Society of Cardiology Guidelines.[18] Subgroups were stratified into those at medium to high risk and those at very high risk according to these guidelines. It should be noted that once an individual has diabetes, he or she is assessed as having at least "medium" risk of cardiovascular disease,[18] and most participants in ADVANCE had high or very high risk. In the event 5803 and 5337 patients were defined as medium–high risk and very high risk, respectively.[17] Blood pressure reductions at the end of 4.3 years of follow-up were similar in the 2 groups, and there was no heterogeneity in the treatment effects across these risk groups for any of the major clinical outcomes (all $P > 0.10$; Fig. 3).[17]

Active treatment with perindopril–indapamide prevented 5 major vascular events, 49 renal events, 4 cardiovascular deaths, and 8 all-cause deaths for every 1000 medium-high risk patients treated for 5 years compared with 12, 54, 15, and 8 such events or deaths for very high-risk patients. Thus, the absolute risk reductions were considerably greater in the very high-risk group.[17]

JOINT EFFECTS OF BLOOD PRESSURE LOWERING AND INTENSIVE GLUCOSE CONTROL ON MAJOR CLINICAL OUTCOMES

Because ADVANCE was planned as a factorial trial of routine blood pressure lowering and intensive glucose control, we were able to assess the magnitude and independence of the effects of blood pressure lowering with perindopril–indapamide and intensive glucose control with the gliclazide-MR–based regimen in this large cohort of 11,140 patients with type 2 diabetes.

Recently published analyses have confirmed that there was no interaction between the effects of these 2 interventions for any of the prespecified clinical outcomes (all $P > 0.1$).[19] Thus the separate effects of blood pressure lowering with perindopril-indapamide and of the intensive gliclazide MR-based glucose control regimen appeared to be additive on a log scale for all-cause mortality, cardiovascular death and major renal outcomes.[19] Indeed, when compared with the group receiving neither intervention, the joint effects of the 2 interventions reduced the risks of all-cause mortality by 18%, of

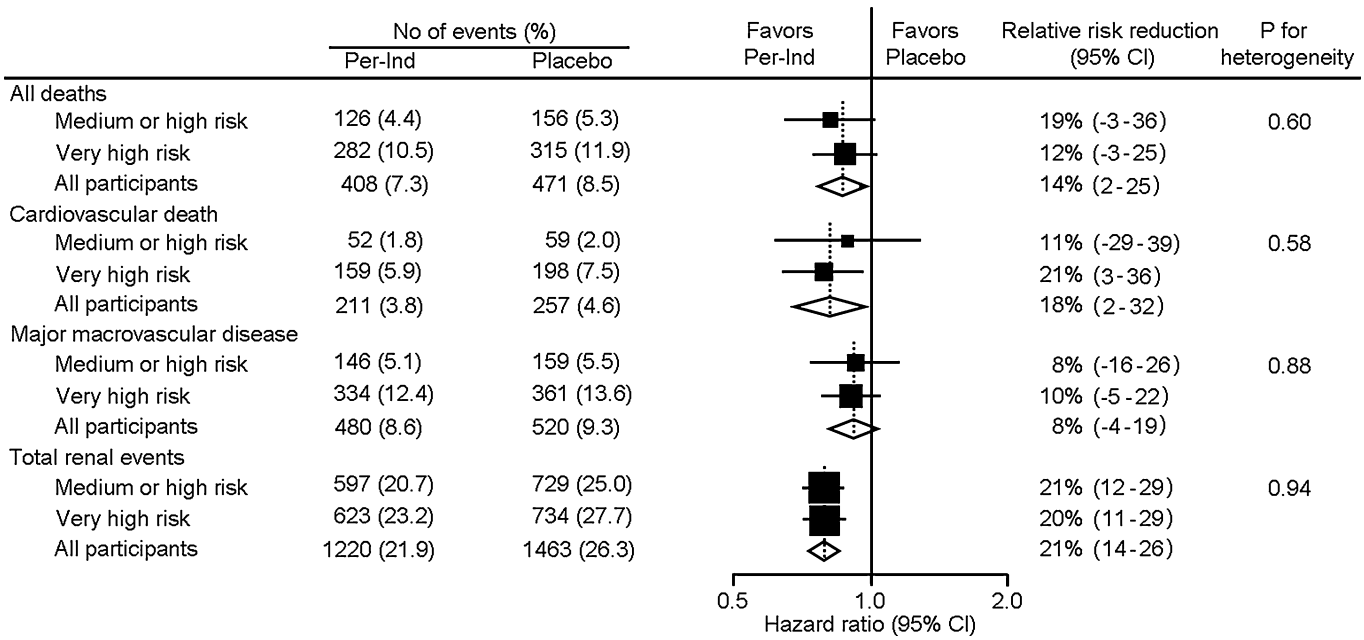

FIGURE 3. Effects of blood pressure lowering on major clinical outcomes according to absolute risk. Conventions as for Figure 2.

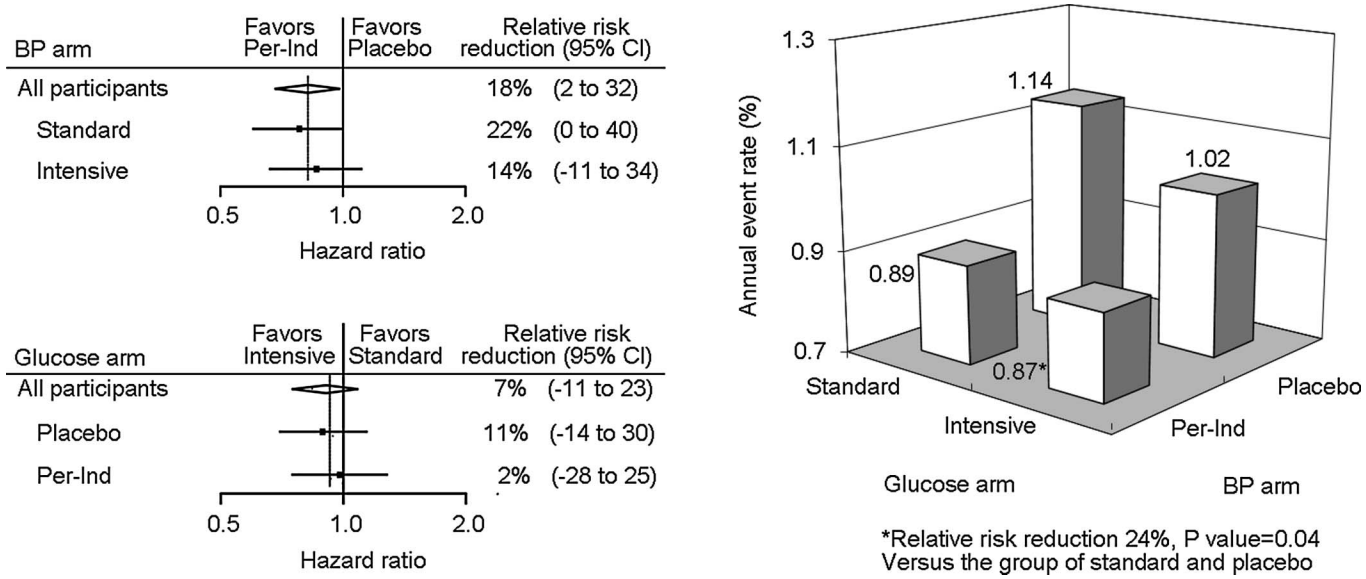

FIGURE 4. Combined effects of blood pressure lowering and intensive glucose control strategy on the incidence of cardiovascular death. Incidence of cardiovascular death is presented as the annual event rate (%) by the four randomized treatment groups: intensive glucose control and perindopril–indapamide (Per–Ind), standard glucose control and perindopril–indapamide, intensive glucose control and placebo and standard glucose control and placebo. Conventions as for Figure 2.

cardiovascular mortality by 24% (Fig. 4), and of new or worsening nephropathy by 33%.[19]

Thus, the separate effects of blood pressure lowering with perindopril–indapamide and of the intensive gliclazide-MR–based glucose control regimen were independent of one another and, when combined, produced additional reductions in major clinical outcomes, confirming the importance of a multifactorial approach for the management of patients with type 2 diabetes.[19]

INTERPRETATION AND DISCUSSION

These results demonstrate substantial consistency in the benefits conferred by blood pressure lowering with the fixed combination of perindopril and indapamide among the patients with type 2 diabetes participating in the ADVANCE trial. There were very similar reductions in all-cause mortality, cardiovascular death, major macrovascular events, and renal events in a wide variety of subgroups categorized according to baseline characteristics including blood pressure, age, albuminuria and renal function, cognition, and total cardiovascular risk. This suggests that the benefits observed in this clinical trial should be broadly generalizable to a very broad cross section of patients with type 2 diabetes at the community level.

The generalizability of the results observed with perindopril–indapamide in ADVANCE is also strongly supported by the similarity in the baseline characteristics of the ADVANCE cohort, with those reported in a number of observational studies at community level,[20–23] as shown in Table 2.

As can be seen in Table 2, the baseline blood pressures, age at entry, presence of cardiovascular disease, degree of nephropathy, or albuminuria seen in ADVANCE are all very representative of levels observed in community studies.

Another salient lesson from ADVANCE is the importance of a multifactorial approach for the management of patients with type 2 diabetes, with 2 essential core elements being routine blood pressure lowering, irrespective of the presence or absence of hypertension, and more intensive glucose control, with a practice based, progressive regimen such as the gliclazide-MR–based strategy used in this trial. Plainly, it is also important to address cholesterol lowering, cessation of smoking, and weight reduction wherever

TABLE 2. Baseline Characteristics for the ADVANCE Participants and Other Cross-Sectional Studies

	ADVANCE	Berthold et al[20] (Germany)	AusDiab[21] (Australia)	DEPAC[22] (Europe)	ENTRED[23] (France)
Age	66 years	65 years	64 years	62 years	65 years
HbA1c	7.5%	7.3%	7.3%	7.7%	7.2%
BMI	28 kg/m^2	29 kg/m^2	30 kg/m^2	31 kg/m^2	28 kg/m^2
SBP	145 mm Hg	143 mm Hg	144 mm Hg	141 mm Hg	140 mm Hg
Duration of diabetes	7 years	7 years	8 years	10 years	11 years
Macrovascular disease	32%	34%	29%	>31%	>21%

BMI = body mass index, SBP = systolic blood pressure.

applicable, for optimal benefits in patients with type 2 diabetes who are at such high risk of vascular disease, as demonstrated in the steno 2 trial.[24]

It is salutary to consider the benefits of blood pressure lowering obtained with perindopril–indapamide in the context of other major trials of blood pressure lowering in type 2 diabetes. The earliest major trial to report the benefit of tighter blood pressure control in patients with type 2 diabetes, the UKPDS,[4] was restricted to hypertensive patients with diabetes. Despite this, it was unable to demonstrate significant reductions in all-cause mortality, renal outcomes, or coronary outcomes, all of which were significantly reduced in ADVANCE, even though this trial included both normotensive and hypertensive patients with diabetes.[8] The second major trial to demonstrate the benefits of blood pressure lowering with ACE inhibitor therapy in patients with type 2 diabetes, the Micro-HOPE trial, did reduce all-cause mortality, cardiovascular death, and overt nephropathy in the same way as ADVANCE, but it was unable to prevent the onset of microalbuminuria, so important for primary prevention.[25] Furthermore, the benefits reported in ADVANCE were observed on top of background ACE inhibitor therapy which was not permitted in the HOPE trial.[8,25,26] Subsequently, studies using angiotensin receptor blockers in patients with nephropathy due to type 2 diabetes did report significant renoprotection, but were unable to demonstrate any reductions in mortality or in major cardiovascular outcomes.[27,28] More recently, the use of angiotensin receptor blockers was unable to provide any significant reduction in the primary composite outcome or in mortality compared with placebo, in patients with cardiovascular disease or high-risk type 2 diabetes.[29,30]

Thus, the results obtained in the blood pressure lowering arm of ADVANCE clearly extend previous evidence and demonstrate that the fixed combination of perindopril and indapamide reduces mortality, cardiovascular events, and renal outcomes in a broad cross-section of patients with type 2 diabetes, on top of other cardioprotective therapies, and independent of baseline blood pressure.

CONCLUSIONS

The evidence gathered in this article, much of it previously published in separate articles elsewhere, clearly demonstrates that routine blood pressure lowering with the fixed combination of perindopril and indapamide was well tolerated and that the relative risk reductions obtained with this treatment were consistent across a broad cross section of patients with type 2 diabetes, regardless of initial blood pressure, of age, of stage of kidney disease, of cognitive function, and of total cardiovascular risk. The evidence also demonstrates that the reductions in absolute cardiovascular risk are greater in those with higher initial risk, as defined by the European Society of Hypertension/European Society of Cardiology Guidelines 2007 guidelines, and that they are also greater in those over the age of 75 and those with chronic kidney disease.

Furthermore, comparison with surveys of patients with type 2 diabetes in the community across the world, suggests that the participants in ADVANCE are very representative of typical patients with type 2 diabetes presenting in general clinical practice, so that the benefits described here should be broadly applicable across most populations worldwide. Our results also confirm the importance of multifactorial regimens that include routine blood pressure lowering and more intensive glucose control. Finally, if the joint benefits obtained in ADVANCE with perindopril–indapamide and with the gliclazide MR–based regimen were applied to all 250 million people with type 2 diabetes alive today, close to 2 million deaths would be avoided in the next 5 years.

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