Brief description of patient problem/setting (summarize the case very briefly)

Pt is a 62 yo F on a triple anti-htn therapy (lisinopril, hydrochlorothiazide, and amlodipine) with persistent htn urgency across multiple visits (187/107, 230/100, 209/106) who states she is compliant with her medication regiment. She is experiencing recurrent headaches x1 year and her EKG today reveals LVH and ischemic changes.

Search Question: Clearly state the question (including outcomes or criteria to be tracked)

"For patients with resistant hypertension, how does universal vs. targeted primary aldosteronism (PA) screening affect MACE and all-cause mortality?"

Question Type: What kind of question is this?

√ Screening √ Diagnosis √ Prognosis

Study type: Assuming that the highest level of evidence to answer your question will be meta-analysis or systematic review, what other types of study might you include if these are not available (or if there is a much more current study of another type)? Please explain your choices.

Prospective cohort study - A very appropriate study design to look at the association between PA and poor outcomes (MACE and all-cause mortality). A prospective cohort study could directly compare universal vs. targeted screening in patients with resistant hypertension and determine which approach leads to lower rates of MACE and all-cause mortality.

Retrospective cohort study - This design would assess the effect of PA screening on MACE and all-cause mortality. Using existing medical records of 10,000 patients, you would group patients based on whether they were screened for PA or not screened and then look back to determine the incidence of MACE and all-cause mortality in each group.

PICO search terms:

Population	Intervention	Comparison	Outcome
Resistant Hypertension	Universal Screening	Targeted Screening	Major adverse cardiovascular events (MACE)
Treatment-resistant hypertension	Primary aldosteronism screening	Guideline-based screening	Cardiovascular mortality
Secondary hypertension	Aldosterone-renin ratio screening	Selective screening	All-cause mortality
			Stroke
			Myocardial infarction

Search tools and strategy used:

Please indicate what databases/tools you used, provide a list of the terms you searched together in each tool, and how many articles were returned using those terms and filters. Explain how you narrowed your choices to the few selected articles. For example, if your search returned 25 articles among the several databases used, what was the process used to determine which four articles to use?

PubMed

Search Terms - ("Hypertension, Resistant"[Mesh] OR "resistant hypertension") AND ("Primary Aldosteronism"[Mesh] OR "primary aldosteronism") AND ("Screening"[Mesh] OR "Mass Screening"[Mesh] OR "universal screening" OR "targeted screening" OR "selective screening") AND ("Mortality"[Mesh] OR "Cardiovascular Diseases"[Mesh] OR "major adverse cardiovascular events" OR "MACE" OR "all-cause mortality")

Results - 22

Selection criteria - I saw a retrospective cohort study following over 100,000 people with hypertension and looked at the rates of PA screening. This is a robust data set, so any insights gleaned from it should be analyzed.

Trip Database

Search Terms - Primary aldosterone “screening”

Results - 13

Selection Criteria - I saw an article comparing the rates of MACE and end-organ damage in pts w/ PA compared to essential htn. This article is a systematic review and meta-analysis, reflecting the highest level of evidence. The topic directly relates to my PICO, to look at the relationship between PA, MACE/all-cause mortality, and how screening interventions can influence these rates.

Google Scholar

Search Terms - Primary aldosterone screening "meta analysis" "MACE"

Results - 3,550

Selection Criteria- I found a meta-analysis reviewing the prevalence of MACE in PA after MRA treatment of adrenolectomy. This directly relates to my PICO question and represents the highest level of evidence possible.

Results found:

Identify at least 3 articles (or other appropriate reputable sources) that answer your specific question with the highest available level of evidence (you will probably need to look at more than 3 articles to get the 3 most focused and highest-level articles to address your question). Please make sure that they are Medline indexed.

In addition to providing the hyperlinks, the full-length articles (PDFs) must also be attached in Brightspace.

Please post the citation and abstract for each article (to include the journal and authors’ names and date) and say why you chose it. Please also note what kind of article it is (e.g. meta-analysis, cohort study, or independent blind comparison with gold standard of diagnosis, etc.).

At the bottom of each abstract, please comment on what your key points are from this article (including any points or concepts included in the article, but not present in the abstract – i.e. make the concepts understandable to the reader) Please note that if the evidence is not in the abstract, you must clearly summarize the evidence in your posting.

Screening Rates for Primary Aldosteronism in Resistant Hypertension: A Cohort Study

Gilad Jaffe, Zachary Gray, Gomathi Krishnan, Margaret Stedman, Yuanchao Zheng, Jialin Han, Glenn M. Chertow, John T. Leppert, and Vivek Bhalla vbhalla@stanford.edu **Author Info & Affiliations**

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Abstract

Resistant hypertension is associated with higher rates of cardiovascular disease, kidney disease, and death than primary hypertension. Although clinical practice guidelines recommend screening for primary aldosteronism among persons with resistant hypertension, rates of screening are unknown. We identified 145,670 persons with hypertension and excluded persons with congestive heart failure or advanced chronic kidney disease. Among this cohort, we studied 4660 persons ages 18 to <90 from the years 2008 to 2014 with resistant hypertension and available laboratory tests within the following 24 months. The screening rate for primary aldosteronism in persons with resistant hypertension was 2.1%. Screened persons were younger (55.9±13.3 versus 65.5±11.6 years; *P*<0.0001) and had higher systolic (145.1±24.3 versus 139.6±20.5 mm Hg; *P*=0.04) and diastolic blood pressure (81.8±13.6 versus 74.4±13.8 mm Hg; *P*<0.0001), lower rates of coronary artery disease (5.2% versus 14.2%; *P*=0.01), and lower serum potassium concentrations (3.9±0.6 versus 4.1±0.5 mmol/L; *P*=0.04) than unscreened persons. Screened persons had significantly higher rates of prescription for calcium channel blockers, mixed α/β-adrenergic receptor antagonists, sympatholytics, and vasodilators, and lower rates of prescription for loop, thiazide, and thiazide-type diuretics. The prescription of mineralocorticoid receptor antagonists or other potassium-sparing diuretics was not significantly different between groups (*P*=0.20). In conclusion, only 2.1% of eligible persons received a screening test within 2 years of meeting criteria for resistant hypertension. Low rates of screening were not due to the prescription of antihypertensive medications that may potentially interfere with interpretation of the screening test. Efforts to highlight guideline-recommended screening and targeted therapy are warranted.

Why I chose this article: RCTs are typically not performed to identify screening guidelines because it would be unethical to withhold a beneficial resource from suffering patients. Therefore, this retrospective cohort study of 145,670 is a great resource to look at screening rates of PA amongst pts with resistant htn and the effect of diagnosing PA on MACE and all-cause mortality.

What kind of article is it: Retrospective Cohort

Key Points: PA is estimated to account for up to 20% of resistant htn cases. There were two criteria for resistant htn in this study: 1) BP ≥140/90 on ≥2 occasions despite 3 anit-htn drug classes (including a diuretic) for ≥21 consecutive days or 2) Prescription of ≥4 anti-htn drug classes regardless of blood pressure control. Of the 145,670 pts in the cohort, ~3.2% of pts met these criteria (4,660 people). These data reveal profound rates of underscreening and substantial delays in screening. Of the 4,660 who fit the criteria, only 2.1% (97) of them received screening for PA w/in 24 months of meeting the criteria. Among those who were screened, the median time to screening was 145 days (25th-75th percentile: 24-346 days).

Researchers identified key associations between who was and who was not screened. Pts who were screened were younger (55.9 vs. 65.5 yo), had higher BP (145/82 vs. 140/74), lower serum potassium (3.9 vs. 4.1), and lower rates of CAD (5.2 vs. 14.2%). Many providers associate PA w/ lower levels of serum potassium despite guidelines emphasizing that most pts w/ PA are normokalemic (50-82%). Increased screening amongst pts with lower rates of CAD represents a critical lapse in understanding, as PA increases CV risk independent of BP.

Researchers found that medication use did not significantly influence who was screened for PA, challenging the common reason providers cite for withholding screening. Despite the potential for false-negative results, patients not taking ACE inhibitors or diuretics still had a very low PA screening rate of 1.7%. Current guidelines now recommend screening for PA even in patients taking these medications. Socioeconomic barriers may also play a role, as 40.2% of the patients screened had private insurance vs. 24.8% w/ government funded insurance.

Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: a systematic review and meta-analysis

Silvia Monticone [1], Fabrizio D'Ascenzo [2], Claudio Moretti [2], Tracy Ann Williams [3], Franco Veglio [1], Fiorenzo Gaita [2], Paolo Mulatero [4] 2018 Jan6

Abstract

Background: There is conflicting evidence, relying on heterogeneous studies, as to whether aldosterone excess is responsible for an increased risk of cardiovascular and cerebrovascular complications in patients with primary aldosteronism. We aimed to assess the association between primary aldosteronism and adverse cardiac and cerebrovascular events, target organ damage, diabetes, and metabolic syndrome, compared with the association of essential hypertension and these cardiovascular and end organ events, by integrating results of previous studies.

Methods: We did a meta-analysis of prospective and retrospective observational studies that compared patients with primary aldosteronism and essential hypertension, to analyse the association between primary aldosteronism and stroke, coronary artery disease (as co-primary endpoints), atrial fibrillation and heart failure, target organ damage, metabolic syndrome, and diabetes (as secondary endpoints). We searched MEDLINE and Cochrane Library for articles published up to Feb 28, 2017, with no start date restriction. Eligible studies compared patients with primary aldosteronism with patients with essential hypertension (as a control group) and reported on the clinical events or endpoints of interest. We also compared primary aldosteronism subtypes, aldosterone-producing adenoma, and bilateral adrenal hyperplasia.

Findings: We identified 31 studies including 3838 patients with primary aldosteronism and 9284 patients with essential hypertension. After a median of 8·8 years (IQR 6·2-10·7) from the diagnosis of hypertension, compared with patients with essential hypertension, patients with primary aldosteronism had an increased risk of stroke (odds ratio [OR] 2·58, 95% CI 1·93-3·45), coronary artery disease (1·77, 1·10-2·83), atrial fibrillation (3·52, 2·06-5·99), and heart failure (2·05, 1·11-3·78). These results were consistent for patients with aldosterone-producing adenoma and bilateral adrenal hyperplasia, with no difference between these subgroups. Similarly, primary aldosteronism increased the risk of diabetes (OR 1·33, 95% CI 1·01-1·74), metabolic syndrome (1·53, 1·22-1·91), and left ventricular hypertrophy (2·29, 1·65-3·17).

Interpretation: Diagnosing primary aldosteronism in the early stages of disease, with early initiation of specific treatment, is important because affected patients display an increased cardiovascular risk compared with patients with essential hypertension.

Why I chose this article: It directly addresses MACE and all-cause mortality related to PA, a key component of my PICO question.

What kind of article is it: Systematic Review and Meta-analysis

Key Points: The study highlights many important cardiovascular risks associated w/ PA. Pts w/ PA have a 2.58-fold increase in stroke risk and 1.77-fold increase in CAD disease risk compared to pts with essential hypertension after an 8.8 year median follow-up. These increased risks are independent of blood pressure. Pt w/ PA have a 3.52-fold increased risk of Afib, a strong risk factor for stroke. Pts w/ PA have a 2.05-fold increased risk of heart failure independent of BP, suggesting excess aldosterone-mediated cardiac remodeling. There is a 2.29-fold increased risk of LVH for pts w/ PA. Beyond increased CV risk factors, pts w/ PA have increased rates of DM2 and metabolic syndrome, major contributors to all-cause mortality. This indicates the pts w/ resistant hypertension are a high-yield screening population. These increased risks were present regardless of the pts PA subtype: aldosterone-producing adenoma and b/l adrenal hyperplasia. These findings indicate the PA carries substantially higher CV morbidity that can be modified with proper treatment.

Major Adverse Cardiovascular Events in Primary Aldosteronism After Adrenalectomy or Mineralocorticoid Receptor Antagonist Treatment: A Systematic Review and Meta-Analysis

Chien-Wei Huang, MD, Tse-Ying Huang, MD, Ya-Fei Yang, MD, Li-Yang Chang MBBS, Yu-Kang Tu, PhD, Vin-Cent Wu, MD, PhD and Jui-Yi Chen, MD
Originally Published 3 February 2025

Abstract

Background

The object of this study was to investigate the incidence rate of major adverse cardiovascular event (MACE) among patients with primary aldosteronism (PA) after adrenalectomy or mineralocorticoid receptor antagonist (MRA) treatment.

Methods and Results

A systematic review and meta-analysis was conducted by searching PubMed, Embase, Cochrane Library, Web of Science, CINAHL, and Scopus through April 15, 2024. Studies reporting the MACE incidence rate in patients with PA after treatment were included. We adapted the random-effects model and performed subgroup and meta-regression analyses. A total of 20 studies involving 16 927 patients with PA were included. There were 5939 patients with PA who underwent adrenalectomy. A total of 10 474 patients received MRA treatment. Additionally, 546 patients received either adrenalectomy or MRA treatment. The pooled incidence rate of MACE among patients with PA after treatment was 2.20/100 patient-years (95% CI, 1.70–2.80), higher than that of non-PA hypertension (1.20/100 patient-years [95% CI, 0.70–2.10]). Patients with PA after adrenalectomy had a lower MACE incidence rate (2.00/100 patient-years [95% CI, 1.40–2.60]) compared with those undergoing MRA treatment (3.30/100 patient-years [95% CI, 2.40–4.10], P=0.017). Advanced age (coefficient: 0.071, P<0.001) and diabetes (coefficient: 0.070, P=0.001) increased the risk of posttreatment MACE. A curvilinear dose–response relationship between the posttreatment plasma renin activity and the MACE incidence was observed, with the lowest risks at plasma renin activity of 1.0 to 2.0 ng/mL per hour ($P_{nonlinearity}$<0.001).

Conclusions

The MACE incidence in treated patients with PA was 2.20 per 100 patient-years, higher than in patients with hypertension without PA. Maintaining posttreatment plasma renin activity between 1.0 and 2.0 ng/mL per hour appears crucial for minimizing cardiovascular risk. Adrenalectomy proved more effective than MRA treatment in reducing MACE risk. Advanced age and diabetes significantly increased the risk of posttreatment MACE.

Why I chose this article: This study includes 16 927 patients with PA and looks at CV outcomes in medically and surgically treated PA.

What kind of article is it: Systematic Review and Meta-analysis

Key Points:

Despite achieving similar BP levels, PA pts treated w/ MRAs had nearly double the MACE incidence rate compared to non-PA hypertension (2.20 vs. 1.20 per 100 pts years). This seems contrary to the belief that MRAs are the tx of choice for PA. This is due to the targeting of blood pressure as the outcome of interest in txing PA. The critical biomarker for cardiovascular risk reduction is post-treatment plasma renin levels. The research demonstrates a curvilinear dose-response relationship between post-treatment plasma renin levels and MACE incidence. The lowest cardiovascular risk was found with plasma renin activity of 1.0 - 2.0 ng/ml/hour. Alternatively, it was found that pts with persistently suppressed renin (<1 ug/L/h) on an MRA had a 2.83-fold higher risk for MACE compared to essential htn. The researches suggest renin-guided MRA titration as standard practice but it is rarely implemented. It is also found that current MRA doses are too low and pts would benefit from highter doses.

For pts w/ u/l adrenal hyperplasia or aldosterone-secreting adenomas, adrenalectomy was found superior to MRA therapy in reducing MACE. Pts who underwent adrenalectomy had a rate of MACE at 2.0 per 100 patient-years. Compared to MRA treatment, which saw MACE at 3.30 per 100 patient-years. This data highlights the importance of proper PA diagnosis because a pt w/ u/l disease may opt for an adrenelectomy which will substantially increase their mortality. It is not enough to add an MRA on as a 4th line anti-htn agent and claim success when the pts BP decreases.

What is the clinical "bottom line" derived from these articles in answer to your question?

In pts w/ resistant htn, current evidence reveals a critical gap between guideline recommendations and clinical practice that results in preventable CV morbidity and mortality. Despite ASCVD being the number one contributor to mortality in the US, we do a terrible job at identifying pts w/ PA. The cohort study from Jaffe and colleagues reveals that PA represents approximately 20% of pts w/ resistant htn. Despite PA accounting for approximately 1 in 5 pts w/ resistant htn, only ~2% of pts in the Jaffe study were screened for it. The systematic review and meta-analysis from Monticone and colleagues clearly demonstrate there are increased rates of MACE and all–cause mortality risk for pts w/ PA. A robust update in clinical practice, universal screening guidelines, and treatment guidelines can save thousands of lives. Despite the obvious hazard of PA, an evidence gap currently exists, as there is no large-scale study on universal vs. targeted screening and the impact on MACE or all-cause mortality.

Even if screening guidelines were updated, our treatment protocols need improvement as well. Increased MACE and all-cause mortality persist in pts w/ PA even when BP is controlled w/ an MRA. The Huang and colleagues study suggests that normalizing renin levels is the key metric that improves outcomes for pts w/ PA, not BP.

These findings support universal screening of resistant htn pts for PA rather than selective screening based on outdated criteria like hypokalemia. The current targeted screening misses upwards of 98% of cases because most patients are normokalemic. For clinicians to best serve their patients, staying up to date on clinical guidelines is critical.

References

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