Type 2 Diabetes: Medication Management & Patient-Centered Lifestyle Modification Support

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AMERICAN ACADEMY OF FAMILY PHYSICIANS

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The content of my material/presentation in this CME activity will include discussion of unapproved or investigational uses of products or devices as indicated: Metformin: It's use for prevention of progression of prediabetes to overt diabetes will be discussed.

Alisa C. Nance, MD

Medical Director, Piedmont Healthcare and Piedmont Community Health Collaborative ACO

Dr. Nance attended the University of North Carolina - Chapel Hill graduating in 1992 with a degree of BS Pharmacy. She attended Wake Forest University School of Medicine and graduated in 1996. She completed her residency in 1999 at Memorial Hermann Southwest in Houston, TX as chief-resident. She has been employed with Piedmont Healthcare multi-specialty group in Statesville, NC since 1999 and has served on their Board of Directors for ten years. She opened her own practice, Nance Family Medicine in 2005. She completed her Diplomat designation with the National Lipid Association in 2008. Since June of 2016, Dr. Nance has served as Medical Director for both Piedmont Healthcare and the newly formed Piedmont Community Health Collaborative ACO. She lives in the hometown where she grew up, giving back to her community. She is married to her husband, Tom and has two sons.

Learning Objectives

1. Utilize the American Diabetes Association general recommendations for anti-hyperglycemic therapy in T2DM.
2. Apply shared decision-making models to develop comprehensive lifestyle modification plans that are tailored for each patient's unique characteristics and heath profiles, including cultural considerations and dietary preferences.
3. Assess and re-assess patients' individual profiles and preferences as treatment plans develop and evolve.

Prevalence

Diabetes

- 29.1 million US citizens
  - 9.3% of U.S. population
    - **Diagnosed:** 21 million
    - **Undiagnosed:** 8.1 million

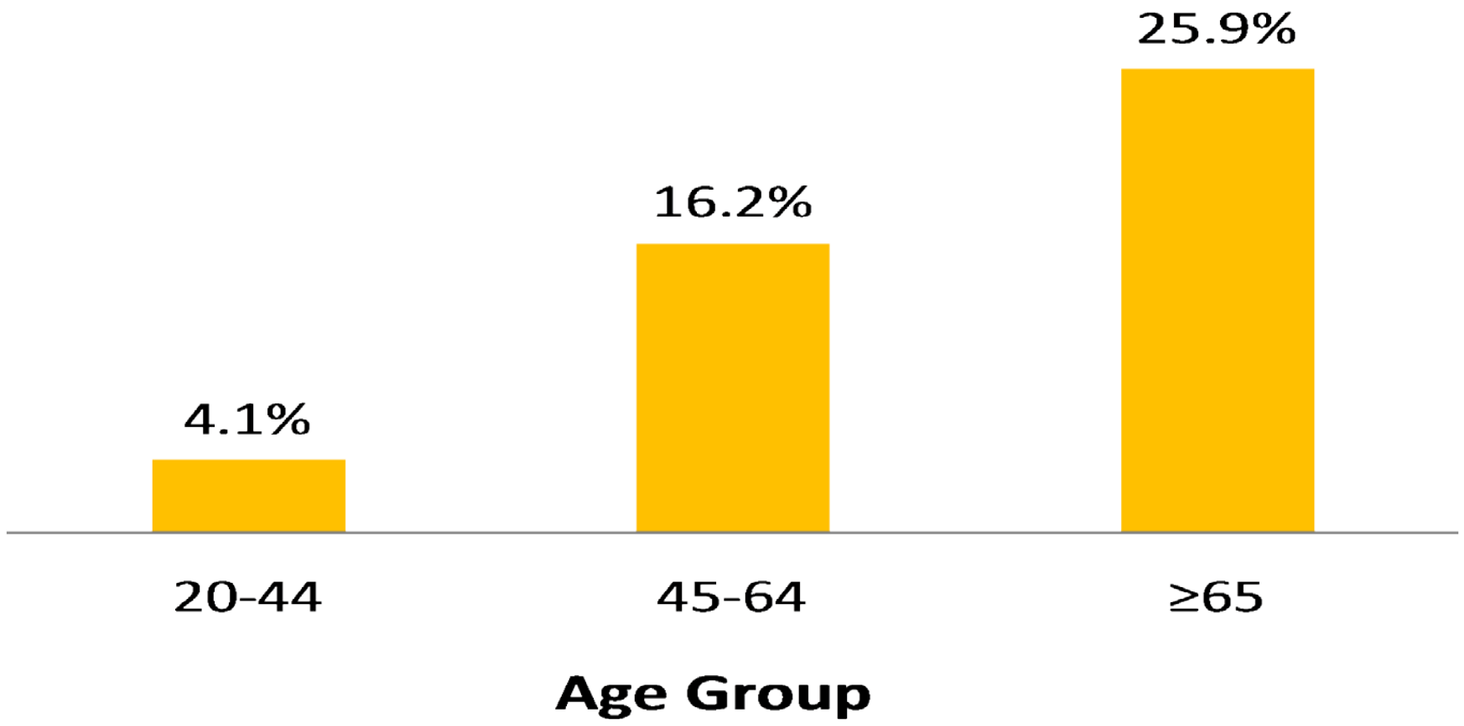
Increase of 3.3 million people over 2010!

Prediabetes

- 86 million US Adults
  - 37% of U.S. population
  - **51% of those 65 years or older!**

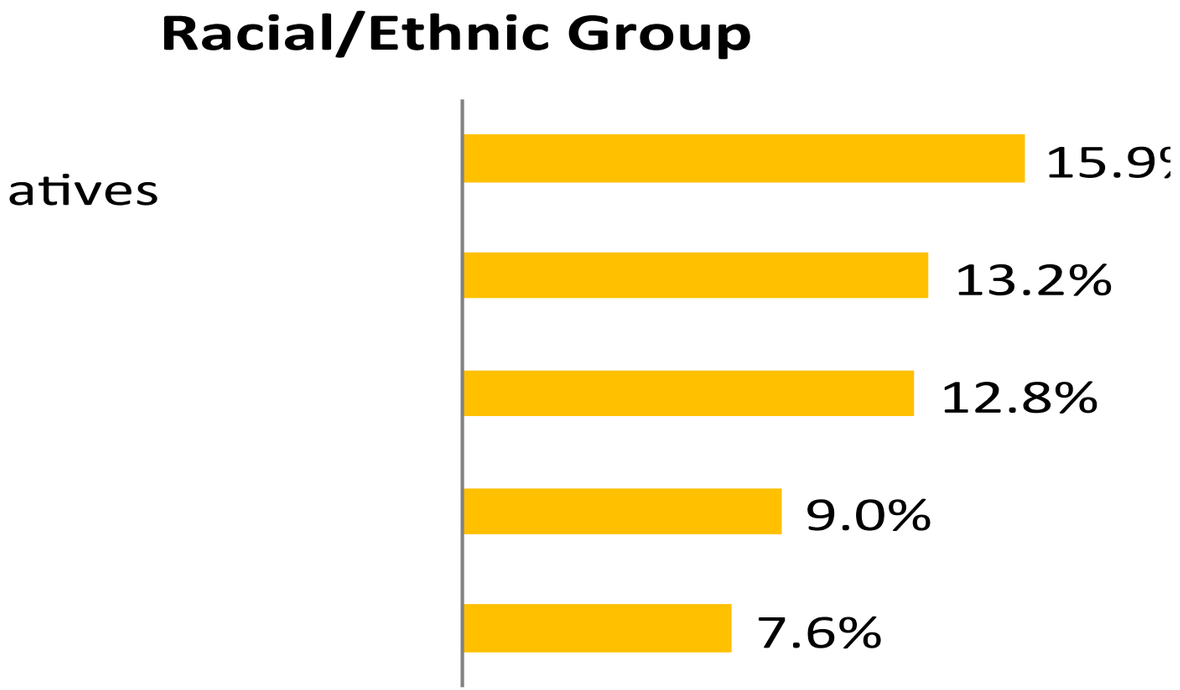
National Diabetes Statistics Report, 2014. Atlanta: Centers for Disease Control and Prevention; 2014. Available at http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf

Number of People 20 Years or Older With Diagnosed and Undiagnosed Diabetes, by Age Group, United States, 2012 (percentage)



National Diabetes Statistics Report, 2014. Atlanta: Centers for Disease Control and Prevention; 2014. Available at http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf

Racial and Ethnic Differences in Diagnosed Diabetes in People Aged 20 years or Older, United States, 2010-2012



National Diabetes Statistics Report, 2014. Atlanta: Centers for Disease Control and Prevention; 2014. Available at http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf

Diabetes

Every 24 Hours…

- 4658 new cases of diabetes are diagnosed.
- 200 nontraumatic lower limb amputations are performed.
- 136 people begin treatment for end-stage renal disease.
- 641 people die of diabetes, or diabetes is a contributing cause of death
  - The seventh leading cause of death overall!

National Diabetes Statistics Report, 2014. Atlanta: Centers for Disease Control and Prevention; 2014. Available at http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf

Every 5 Minutes…

- 16 new cases of diabetes diagnosed.
- 2 people die of diabetes-related causes

ADA Evidence Grading System

Level of Evidence	Description
A	**Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered**
B	**Supportive evidence from well-conducted cohort studies**
C	**Supportive evidence from poorly controlled or uncontrolled studies** **Conflicting evidence with the weight of evidence supporting the recommendation**
E	**Expert consensus or clinical experience**

Standards of Medical Care in Diabetes—2016 : Summary of Revisions. *Diabetes Care*. 2016;39(Supplement 1):S4-S5. doi:10.2337/dc16-S003.

Diagnosis of Diabetes Mellitus

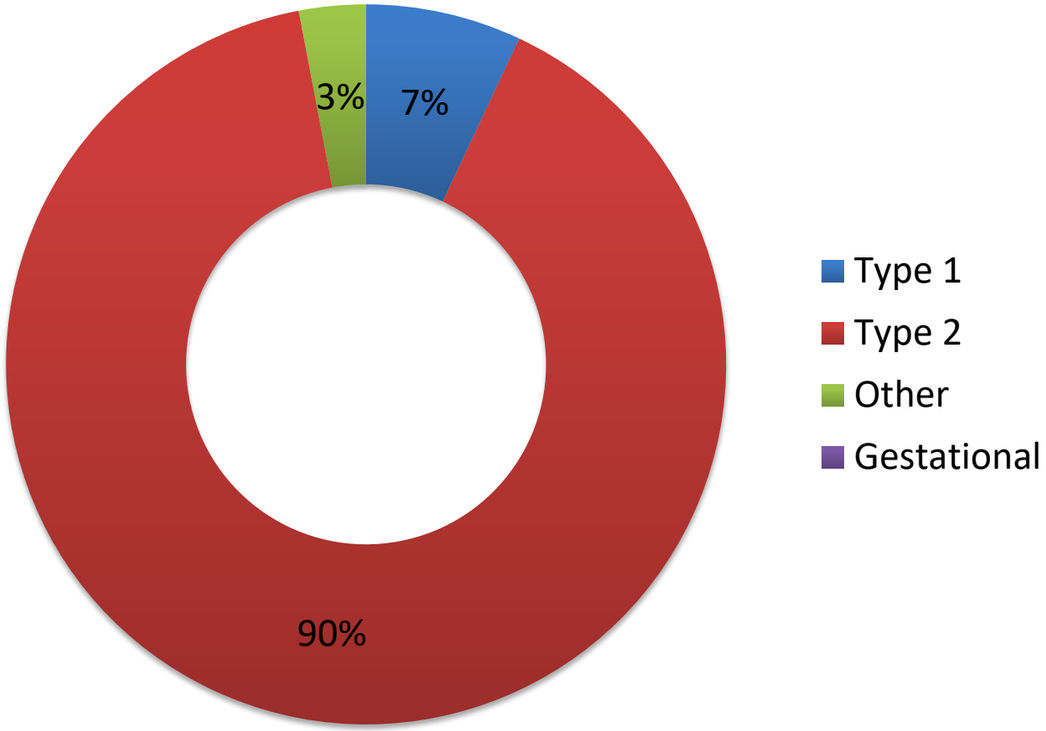
1. FPG ≥126 mg/dL (7.0 mmol/L)
   - Fasting = no calories for at least 8 hours
2. 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L)
   - During oral glucose tolerance test (OGTT)
3. Hemoglobin A1C (A1C) ≥6.5%
4. Classic symptoms of hyperglycemia or hyperglycemic crisis, with a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L)

- In absence of unequivocal hyperglycemia, criteria 1 through 3 should be confirmed by repeat testing.
- Only criteria 4 does not require repeat testing
- **NEW in 2016**: Changed the order to make it clear that no one test is preferred over another.

Classification and Diagnosis of Diabetes. *Diabetes Care*. 2016;39(Supplement 1):S13-S22. doi:10.2337/dc16-S005.

Types of Diabetes Mellitus

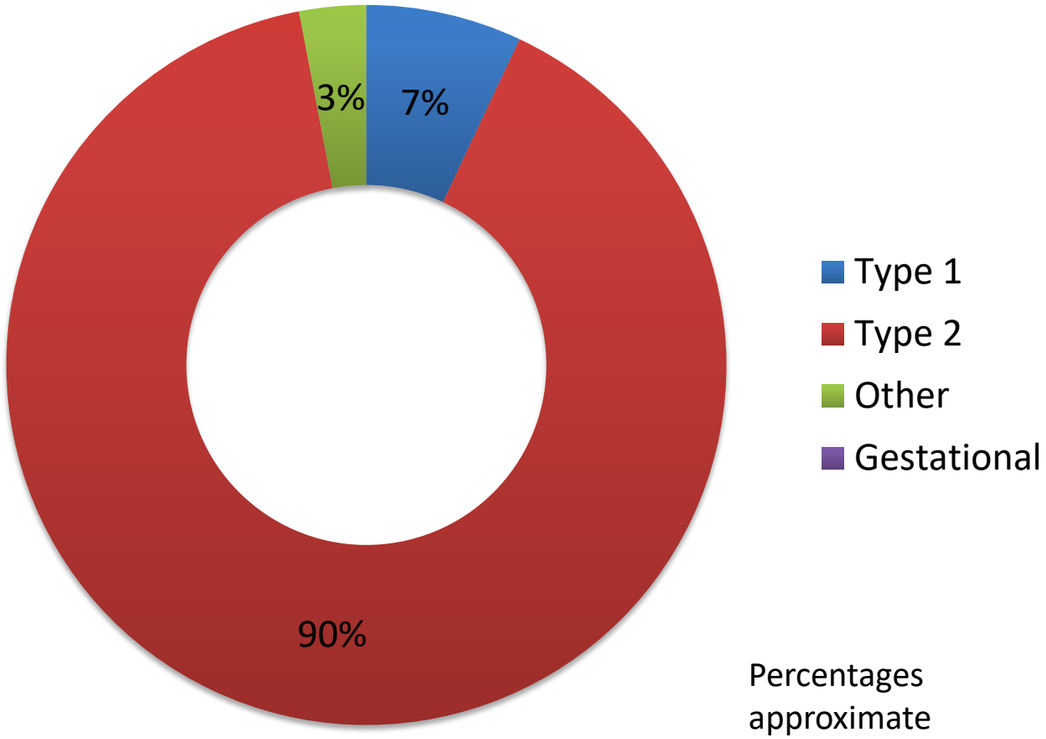
1. Type 1
   - ~ 5 to 10%
2. Type 2
   - ~90 to 95%
3. Gestational Diabetes Mellitus
   - ~7% all pregnancies,
     > 200,000 cases/year
4. Other specific types
   - Monogenic syndromes (<5%), diseases of exocrine pancreas, drug/chemical induced



Classification and Diagnosis of Diabetes. *Diabetes Care*. 2016;39(Supplement 1):S13-S22. doi:10.2337/dc16-S005.

“New” Organization

1. Type 1 *(E10.--)*
   - – Absolute insulin deficiency
     - Immune-mediated
     - Idiopathic
2. Type 2 *(E11.--)*
   - – Insulin resistance + relative insulin deficiency
     - Most obese
3. Gestational *(O24.4-)*
4. Other
   - Monogenic Diabetes Syndromes *(E13.--)*
     - Neonatal Diabetes *(P70.2--)*
     - Maturity-onset diabetes of the young (MODY)
   - Diseases of the exocrine pancreas (Cystic fibrosis,…) *(E08.--)*
   - Drug or chemical induced (steroids,…) *(E09.--)*



Percentages approximate

American Diabetes Association. 2. Classification and Diagnosis of Diabetes. Diabetes Care. 2017 Jan;40(Supplement 1):S11–24.

Pre-Assessment Question

1. Prediabetes is defined as a fasting glucose in the range of 100-125 mg/dL, referred to as Impaired Fasting Glucose (IFG) or an A1C in the range of 5.7% to 6.4%, among other criteria.

   Between these two measures, impaired fasting glucose is a better predictor of subsequent diabetes and cardiovascular disease than is a baseline A1C in the prediabetes range.

   A. True
   B. False

Prediabetes

Impaired Fasting Glucose (IFG) & Impaired Glucose Tolerance (IGT)

- **IFG** = FPG 100 to 125 mg/dL
- **IGT** = 2-hour plasma glucose 140 to 199 mg/dL (after 75 g challenge)
  - Risk factors for diabetes and cardiovascular disease
  - Strongly associated with
    - Obesity
      - Abdominal or visceral
    - Dyslipidemia
      - High triglyceride levels
      - And/or low high-density lipoprotein (HDL)
    - Hypertension

A1C

- A1C = 5.7% to 6.4%
  - Range 6.0% to 6.5%
    - 25% to 50% 5-year incidence of diabetes
    - Relative risk 20 x greater than at A1C = 5.0
  - Baseline A1C a stronger predictor of subsequent diabetes and cardiovascular diseases than fasting glucose

Classification and Diagnosis of Diabetes. *Diabetes Care*. 2016;39(Supplement 1):S13-S22. doi:10.2337/dc16-S005.

Testing for Type 2 DM in Adults

- *Use informal assessment of risk factors or validated tool (B)*
  - *www.diabetes.org/are-you-at-risk*
- All overweight adults with at least one risk factor. (B)
  - BMI ≥25 kg/m^2
  - BMI ≥23 kg/m^2 in Asian Americans
- All patients starting at age 45 years (B)
- If normal, repeat at least every 3 years (C)
- All criteria considered equally appropriate (B)
  - Fasting Plasma Glucose
  - 2-hour plasma glucose (after 75-g glucose) OGTT
  - A1c
- Treat CV risk factors in patients with prediabetes. (B)
- Consider testing in overweight/obese children/adolescents with two or more additional risk factors. (E)

Classification and Diagnosis of Diabetes. *Diabetes Care*. 2017;40(Supplement 1):S11-S24. doi:10.2337/dc17-S005.

Risk Factors (any one)

- A1c ≥ 5.7%, IGT, IFG previously
- Physical inactivity
- First-degree relative with diabetes
- High-risk race/ethnicity
  - African American
  - Latino
  - Native American
  - Asian American
  - Pacific Islander
- Women:
  - Polycystic ovary syndrome (PCOS) or h/o GDM
- Hypertension
  - (≥140/90 mm Hg / on therapy)
- Dyslipidemia
  - HDL <35 mg/dL
  - Triglyceride > 250 mg/dL
- H/o Cardiovascular Disease
- A1C ≥5.7%, IGT or IFG on previous testing
- Other clinical conditions associated with insulin resistance
  - Obesity
  - Acanthosis nigricans

Classification and Diagnosis of Diabetes. *Diabetes Care*. 2017;40(Supplement 1):S11-S24. doi:10.2337/dc17-S005.

Prevention/Delay of Type 2 DM

Patients with Prediabetes:

- Annual monitoring for progression (E)
- (A) referred to intensive behavioral life-style intervention program modeled on the Diabetes Prevention Program (DPP) to achieve and maintain:
  - loss of 7% of body weight
  - Increase moderate-intensity physical activity (brisk-walking) to at least 150 minutes/week
- Technology tools, social networks, distance learning, DVD, mobile apps may be useful in lifestyle modification. (B)
- Based on cost-effectiveness, intervention programs should be covered by third-party payers (B)
- (A) Metformin for prevention (NOT FDA-APPROVED) should be considered, especially in:
  - BMI > 35 kg/m^2
  - Age < 60 years
  - Women with prior gestational DM
  - Rising A1c despite lifestyle intervention
- *B12 monitoring w/ long-term metformin* (B)
- Screening/treatment of modifiable risk factors for CV disease (B)
- Diabetes self-management education and support (B)

5. Prevention or Delay of Type 2 Diabetes. *Diabetes Care*. 2017;40(Supplement 1):S44-S47. doi:10.2337/dc17-S008.

Diabetes Prevention Program Results

- Prevention of diabetes (1996-1999)
  - 3,234 participants, overweight, prediabetes
    - 45% from ethnic/racial minorities at increased risk
  - 4 groups
    - Lifestyle intervention:
      - 7% body weight loss
      - 150 minutes/week of exercise
    - Metformin 850 mg 2 times/day
    - Placebo
    - Troglitazone* (stopped–due to risk of liver damage)

- **3-year risk of developing diabetes**
  - Placebo = 28.9%
  - Metformin = 21.7%
  - Lifestyle intervention = 14.4%
- **Lifestyle vs. Placebo** (RRR = 58%)
  - Most effective in older adults (≥60 years)
    - reduced risk by 71%
  - RRR = 58%,
  - ARR = 14.5%, NNT = 6.9
- **Metformin vs. Placebo**
  - Most effective in young adults (25 to 44 years) with BMI ≥35 kg/m^2
  - Least effective in middle age adults (>45 years)
    - Not significantly better than placebo in older adults (≥60 years)
  - RRR = 31%,
  - ARR = 7.2%, NNT = 13.9

Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346(6):393-403.

Diabetes Prevention Program Outcomes Study

Lifestyle Modification

- Reduced development of DM vs. placebo
  - 34% (RRR)
  - 49% in those 60 years or older (RRR)
  - Delayed type 2 DM by ~4 years
- Reduced cardiovascular risk factors
- Reduced A1C and fasting glucose

Metformin

- Reduced development of DM vs. placebo
  - 18% (RRR)
  - Delayed type 2 DM by ~2 years
- Reduced A1C and fasting glucose

Knowler WC, Fowler SE, Hamman RF, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet*. 2009;374(9702):1677-1686. Erratum in *Lancet*. 2009;374(9707):2054.

Mid-Point Q & A

Comprehensive Medical Evaluation and Assessment of Comorbidities

- Patient-centered communication style to optimize health outcomes/health-related quality of life. (B)
  - Active listening, patient preferences/beliefs.
  - Assess literacy, numeracy, potential barriers to care.
- Comprehensive Medical Evaluation (Initial)
  - Confirm and classify diabetes (B)
  - Detect complications/comorbid conditions(E)
  - Review previous treatment/risk factor control (E)
  - Begin patient engagement in management plan (B)
  - Develop continuing care plan (B)
- Immunizations
  - Routine age-related recommendations (C)
  - Annual influenza ≥ 6 months age (C)
  - Pneumonia vaccine: (C)
    - 2-64 y/o: PPSV23
    - ≥ 65 y/o: PCV13
      - (at least 1 yr after PPSV23)
      - (follow w/ 2nd PPSV23 – at least 1 yr later and 5 yrs after last PPSV23)
  - Hepatitis B, 3 doses:
    - Unvaccinated adults 19-59 y/o (C)
    - Consider in unvaccinated adults ≥ 60 y/o (C)
- Consider screening type 1 patients for autoimmune thyroid/celiac disease shortly after diagnosis. (E)
- People w/ cognitive impairment/dementia, treatment to avoid significant hypoglycemia (B)

Comprehensive Medical Evaluation and Assessment of Comorbidities

- In patients w/ HIV (E)
  - screen for DM & prediabetes with fasting glucose
    - Every 6-12 months before starting antiretroviral tx
    - Every 3 months after starting or changing antiretroviral tx
  - If initial screen normal, recheck every year
  - If prediabetes detected, recheck every 3-6 months
- Anxiety disorders, consider screening:(B)
  - If anxiety/worries (about complications, insulin injections, medications, hypoglycemia) interfere w/ self-management.
  - In those w/ fear, dread, irrational thoughts, avoidance or excessive repetitive behaviors, social withdrawal.
- Depression screening
  - Annually in patients w/ DM, especially if h/o depression. (B)
  - Consider at complication diagnosis/significant change in medical status. (B)

Comprehensive Medical Evaluation and Assessment of Comorbidities

- Disordered Eating
  - Consider reevaluation of treatment for those with symptoms of disordered eating behavior, an eating disorder, or disrupted patterns of eating. (B)
  - Consider screening for disordered/disrupted eating when hyperglycemia and weight loss are unexplained (based on self-reports of behavior related to medications, meal plan, and physical activity). Review treatment plan for effects on hunger/caloric intake. (B)
- Serious Mental Illness
  - Annually screen for prediabetes/DM in those on atypical antipsychotics. (B)
  - If second-generation antipsychotic prescribed for adolescents/adults with DM, carefully monitor for changes in weight, glycemic control, cholesterol level. (C)
  - Incorporate monitoring of DM self-care into treatment goals in people w/ DM and serious mental illness (B)

Lifestyle Management

- Diabetes self-management education (DSME) and support (DSMS)
  - Recommended in all people with DM, to facilitate knowledge, skills and ability necessary at diagnosis and thereafter (B)
  - Measure/monitor health status, quality of life as part of routine care (C)
  - Should be patient-centered, respectful, responsive to preference, needs and values (A)
  - Focused on prevention in prediabetes (B)
  - Can improve outcomes/reduce cost (B)
  - Should be third-party reimbursed (E)
- Medical Nutrition Therapy
  - (see reference)

- Physical Activity
  - Children: (C)
    - ≥ 60 mins/day moderate/vigorous aerobic + muscle/bone strengthening ≥ 3 days/week.
  - Adults w/ type 1(C) and type 2 DM(B):
    - > 150 mins/week moderate intensity over ≥ 3 days with no more than 2 consecutive days without activity.
    - Resistance training 2-3 sessions/week on non-consecutive days.
  - Decrease sedentary behavioral in all.
  - Interrupt prolonged sitting every 30 mins for blood glucose benefits in type 2 (C)
  - Flexibility/balance 2-3 x/week in older adults w/ DM. may consider yoga/tai chi (C)

Lifestyle Management

- Smoking Cessation: Tobacco & e-Cigarettes
  - Advise all patients not to use cigarettes, other tobacco products (A) or e-cigarettes. (E)
  - Include smoking cessation counseling/treatment as a routine part of diabetes care (B)

- Diabetes Distress
  - Routinely monitor for diabetes distress, particularly when treatment targets not met and/or at onset of diabetes complications.

- Psychosocial Assessment and Care
  - Psychosocial care should be integrated with a collaborative , patient-centered approach with goal of optimizing outcomes and health-related quality of life. (A)
  - Psychosocial screening/follow-up: attitudes about illness, expectations of management/outcomes, affect/mood, quality of life, resources (financial, social, emotional), and psychiatric history. (E)
  - Consider assessment for diabetes distress, depression, anxiety, disordered eating, cognitive capacities at diagnosis and periodically (B)
  - Consider screening older adults ≥ 65 for cognitive function/depression screening/treatment (A)

FDA-Approved Diabetes Medications

Insulin / Insulin Releasers

- Secretagogues
  - Sulfonylureas
  - Meglitinides (“glinides”)
- Analogs (Insulin)
  - Rapid/Short/Intermediate/ Long-acting
  - *Inhaled (-unavailable?)*

Euglycemics

- Insulin Sensitizers
  - Biguanides, Thiazolidinediones (TZDs)
- SGLT2 Inhibitors
- α-glucosidase inhibitors
- GLP-1 analogs (subcutaneous)
- DPP4-inhibitors (oral)
- Amylin analogs
- Others
  - Dopamine-receptor agonists
  - Bile acid sequestrants

Sulfonylureas

- 1st Generation
  - chlorpropamide
    - *Diabinese**
  - tolbutamide
    - *Orinase**
  - tolazamide
    - *Tolinase**
- 2nd Generation
  - glimepiride
    - *Amaryl*
  - glyburide
    - *Diabeta **, *Glycron **, *Glynase*
  - glipizide
    - *Glucotrol*

- Stimulate insulin secretion
  - Expected A1C reduction = 1-2%
- Advantages
  - Rapid onset of action
- Disadvantages
  - Hypoglycemia
  - Weight gain (~ 2kg)
  - Poor maintenance of glucose targets

* No longer marketed under brand name.

Nathan DM, Buse JB, Davidson MB, et al. Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy. *Diabetes Care*. 2009;32(1):193 -203

Meglitinides ("Glinides")

- Repaglinide
  - *Prandin*
- Nateglinide
  - *Starlix*

- Stimulate insulin secretion
  - Very similar to sulfonylureas
  - Expected A1C reduction = 0.5-1.5%
- Advantages
  - Rapid onset of action / short duration
- Disadvantages
  - Short duration (mealtime dosing)
  - Hypoglycemia

Pre-Assessment Question

2. Which of the following medication classes can, on average, achieve the greatest decrease in A1C alone?

A. A thiazolidinedione (e.g. pioglitazone)
B. An SGLT-2i (e.g. canagliflozin)
C. A biguanide (e.g. metformin)
D. A DPP-4i (e.g. sitagliptin)
E. A meglitinide (e.g. repaglinide)

Case #1

Mrs. M is a 66-year-old female with a long-standing diagnosis of type 2 diabetes. She has used metformin at a dose of 1000 mg twice daily for 8 years, adding insulin glargine to her regimen 3 years ago. Under your direction, she has titrated the insulin glargine to 40 units at bedtime daily. You have followed Mrs. M closely since her renal function began to worsen 2 years ago. On her recent lab work, you noticed that she now has CKD 3a since her eGFR is now at 40.

Pre-Assessment Question – Case #1

3. What is the most immediate medication course of action, given the finding of worsening renal function in this patient?

A. Stop metformin immediately, adding an SGLT-2 inhibitor to compensate.
B. Decrease her insulin glargine to compensate for lack of renal clearance.
C. Add a DPP-4 inhibitor to improve renal function.
D. Continue metformin at current dose; continuing to closely monitor renal function.
E. Change insulin glargine to rapid-acting insulin three times daily.

Insulin Sensitizers

- Biguanides
  - Metformin
    - *Glucophage, Glucophage XR, Fortamet, Glumetza, Riomet* – liquid
- TZDs
  - Pioglitazone
    - *Actos*
  - Rosiglitazone
    - *Avandia*

Biguanides = Metformin

- Decrease hepatic glucose output
  - Expected A1C reduction = 1-2%
  - Weight neutral, Low risk of hypoglycemia
  - nausea, diarrhea
- Long-term use associated with B12 deficiency
  - Recommend ”periodic monitoring”

CKD stage	eGFR	Metformin dose	Notes
2	60-<90	2550 mg	
3a	45-<60	2000 mg	Monitor renal function closely, avoid if unstable
3b	30-<45	1000 mg	Don’t start metformin, monitor closely, stop if unstable
4	<30	-	DO NOT USE

Adapted from: Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK. Metformin in Patients With Type 2 Diabetes and Kidney Disease: A Systematic Review. *JAMA*. 2014;312(24):2668. doi:10.1001/jama.2014.15298.
* NOT TESTED IN A CLINICAL TRIAL, NOT FROM FDA REVIEW

TZDs

- Sensitize muscle/fat/liver to insulin
  - Expected A1C reduction = 0.5-1.4%
  - Weight gain, fluid retention (CHF)
- Rosiglitazone access restrictions lifted Nov 2013

- NEW 2016:
  - Pioglitazone associated with higher risk of bladder cancer (again).
    - (not Rosiglitazone)
    - 63% increase risk
      - Worse w/ increased dose/duration

Tuccori M, Filion KB, Yin H, Yu OH, Platt RW, Azoulay L. Pioglitazone use and risk of bladder cancer: population based cohort study. *BMJ*. March 2016:i1541. doi:10.1136/bmj.i1541.

Case #2 (Continued)

Mrs. M has remained on metformin and insulin glargine for several more months, with no further significant reduction in her renal function. She continues to have good AM fasting blood sugars averaging around 110 mg/dL. Despite this, her A1c is above goal at 8.2%, and she has noticed that her fasting blood sugars before lunch and dinner are now much higher, averaging 190 mg/dL. She would like to continue to maintain good blood sugar control.

Pre-Assessment Question – Case #2

4. What is the best medication change at this time?

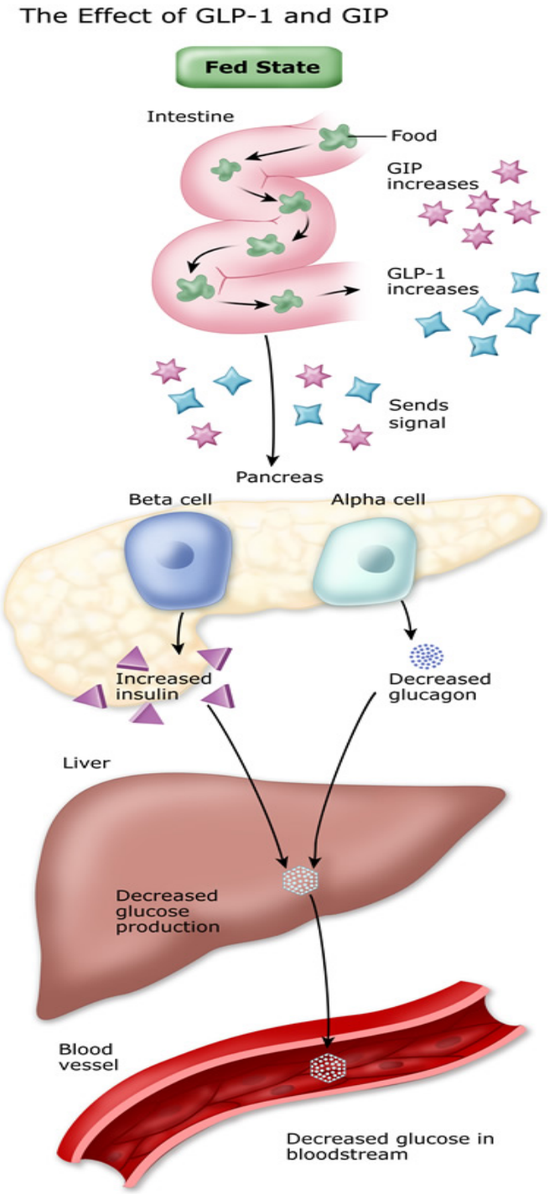
A. Increase her insulin glargine by at least 50% to better control pre-meal blood sugar.
B. Add a GLP-1 (daily or weekly) to achieve a better blood sugar control at least risk of hypoglycemia.
C. Add pre-meal insulin to reduce overall risk of hypoglycemia.
D. Stop metformin because it is likely causing hyperglycemia as a response to metabolic acidosis.
E. Change insulin glargine to rapid-acting insulin three times daily.

Incretins / Incretin Mediators

- GLP-1 Receptor Agonist = (Incretin mimetics)
  - Exenatide
    - *Byetta, Bydureon*
  - Liraglutide*
    - *Victoza*
  - Albiglutide
    - *Tanzeum*
  - Dulaglutide
    - *Trulicity*
- DPP-4 inhibitors = (Incretin enhancers)
  - Sitagliptin
    - *Januvia*
  - Saxagliptin
    - *Onglyza*
  - Linagliptin
    - *Tradjenta*
  - Alogliptin
    - *Nesina*

Incretins

- Intestinal hormones
  - Glucagon-like peptide 1 (GLP-1)
  - Gastric Inhibitory Peptide (GIP)
- Stimulated by eating
  - ↑ insulin/ ↓ glucagon
    - Release insulin in glucose-dependent manner
- Slowed gastric emptying
  - (?) decreased food intake
- Result
  - Lower blood glucose
  - Slowed appearance in circulation



GLP-1-RA (Incretin Mimetics)

- Long-lasting analog of GLP-1
  - Expected A1C reduction = 0.5-1.5%
- Advantages
  - Lowers postprandial glucose
  - Weight loss ~ 2-3 kg/6 months
    - (Liraglutide 3 mg daily (*Saxenda*) FDA-approved for weight loss)
  - Weekly forms (exenatide ER, albiglutide, duraglutide)
- Disadvantages
  - Require subcutaneous injection
  - GI side effects – nausea/vomiting/diarrhea

- Since 2008: all DM drugs must pass CVOT: Cardiovascular Outcome Trials:
- In LEADER trial:
  - Liraglutide v. Placebo v. Standard Care
  - Composite Outcome: MI, Stroke, CV Death
    - 13% Liraglutide group
    - 14.9% Placebo group
    - = 13% RRR -or- 1.9% ARR
  - NNT – prevent 1 event (composite) / 3 yrs = 66
  - NNT-prevent 1 death / 3yrs = 98

GLP-1-RA/Insulin combinations

- NEW in November 2016:
- GLP-1 / Ultra-long insulin combinations
  - Insulin degludec/liraglutide *(Xultophy)*
    - *(Tresiba + Victoza)*
  - Insulin glargine/lixisenatide *(Soliqua)*
    - *(Lantus + Adlyxin)*
- Compare to basal or basal+prandial insulin
  - Expected A1c reduction = 1.2-1.8%
  - Less hypoglycemia

DPP-4 Inhibitors (Incretin enhancers)

- Inhibit Dipeptidyl peptidase 4
  - the enzyme that breaks down GLP-1
  - Expected A1C reduction = 0.5-1.0%
  - Weight neutral, well tolerated
  - Do not cause hypoglycemia (as monotherapy)
  - Increase in upper respiratory infections noted
- FDA Warnings:
  - 2015: Risk of severe joint pain with all DPP-4s
  - 2016: Increased risk of heart failure with saxagliptin or alogliptin) (and combinations including either)
- CVOT: No significant difference vs. placebo

SGLT2 Inhibitors

- Canagliflozin
  - *Invokana*
- Empagliflozin
  - *Jardiance*
- Dapagliflozin
  - *Farxiga*

- Reduces reabsorption of glucose in kidneys, increases urinary glucose excretion
  - Expected A1C reduction = ~0.5-1.0%
- Insulin Independent!
  - Effective in all stages of Diabetes

SGLT2 Inhibitors

- Advantages
  - Once daily dosing.
  - Weight loss
    - ~ 2 kg over 6-12 months
- Disadvantages
  - Require renal dosing!
  - Adverse reactions
    - Dehydration
    - Genital yeast infection
    - Nasopharyngitis
    - Urinary tract infections
    - Increased LDL-C
    - Bladder cancer ?

- FDA Warnings:
  - 2016: strengthened existing warnings of Acute Kidney Injury for Canagliflozin & Dapagliflozin
  - 2015: DKA in Type 2 patients with al SGLT2i

SGLT2 Inhibitors

- CVOT:
- In EMPA-REG Outcome trial:
  - Empagliflozin v. Placebo v. Standard Care
  - Composite Outcome: MI, Stroke, CV Death
    - 10.5% Empagliflozin group
    - 12.1% Placebo group
    - = 14% RRR -or- 1.6% ARR
  - NNT – prevent 1 event (composite) / 3 yrs = 61
  - NNT-prevent 1 death / 3yrs = 39

- NOTE: Cannot directly compare Cardiovascular Outcome Trials for different medications head-to-head!
  - They are all done in different patient populations
  - Different inclusion/exclusion
  - Different baseline A1c, medications, …

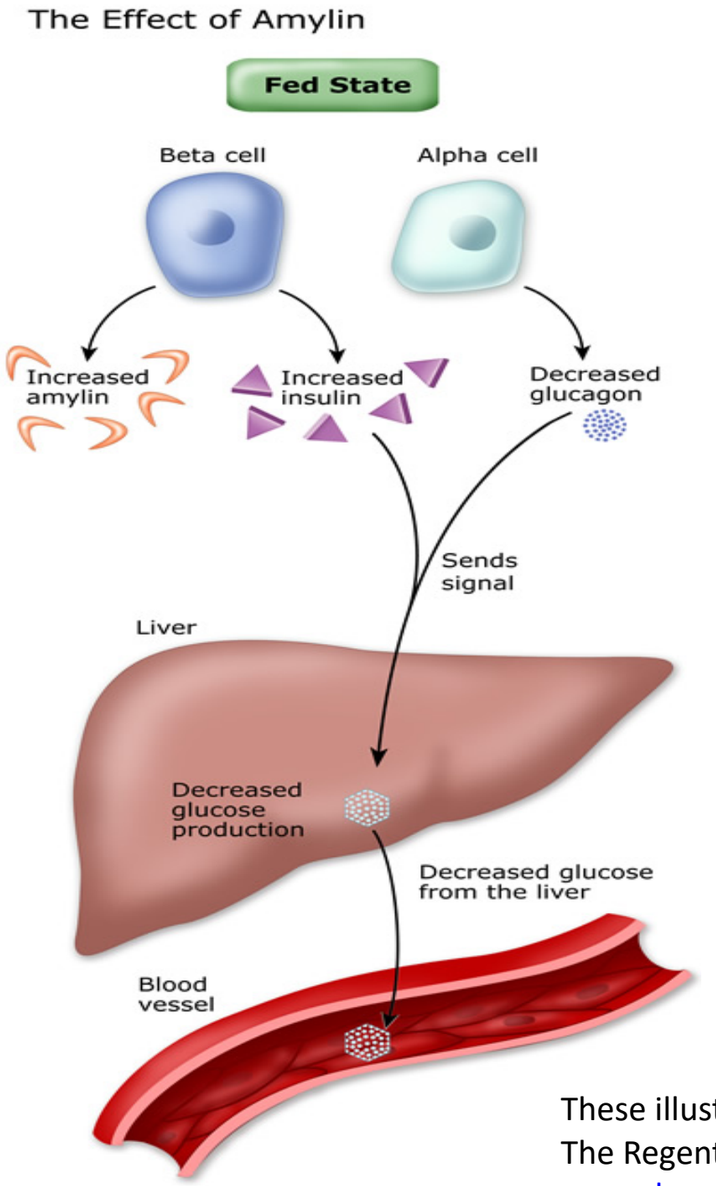
α-glucosidase inhibitors

- Delay carbohydrate digestion in proximal small intestine
  - Expected A1C reduction = 0.5-0.8%
- Advantages
  - Lower postprandial glucose
- Disadvantages
  - GI side effects – flatulence/diarrhea
    - 25-45% of patients discontinue due to side effects

Nathan DM, Buse JB, Davidson MB, et al. Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy. *Diabetes Care*. 2009;32(1):193 -203

Amylin

- AKA Islet Amyloid Polypeptide (IAPP)
- Co-secreted with Insulin
- Binds to brain receptors
  - Inhibits glucagon
  - Delays gastric emptying
  - Promotes satiety
- Amylin analogue
  - Pramlintide
  - Only non-insulin drug approved for Type 1 DM



Pramlinitide

- Synthetic analog of Amylin
  - Expected A1C reduction = 0.5-0.7%
- Advantages
  - Approved for Type 1 and Type 2 Diabetes
- Disadvantages
  - Only approved for use along with insulin
    - Risk of serious hypoglycemia (reduce insulin 50%)
  - Requires subcutaneous injection with meals
  - GI side effect – nausea (~30% of patients)

Nathan DM, Buse JB, Davidson MB, et al. Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy. *Diabetes Care*. 2009;32(1):193 -203

Other Drugs

- Dopamine Receptor Agonist
  - Quick-release Bromocriptine
    - Mechanism unknown
    - Expected A1C reduction = ~0.5%
    - Advantages
      - Minimal risk of hypoglycemia
      - Weight neutral
    - Disadvantages
      - GI adverse effect - nausea
- Bile-acid sequestrants
  - Colesevelam
    - Mechanism unknown
    - Expected A1C reduction = ~0.5%
    - Advantages
      - Also reduces LDL cholesterol
      - Works in GI tract, not systemically absorbed
    - Disadvantages
      - Raises triglycerides

Nathan DM, Buse JB, Davidson MB, et al. Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy. *Diabetes Care*. 2009;32(1):193 -203

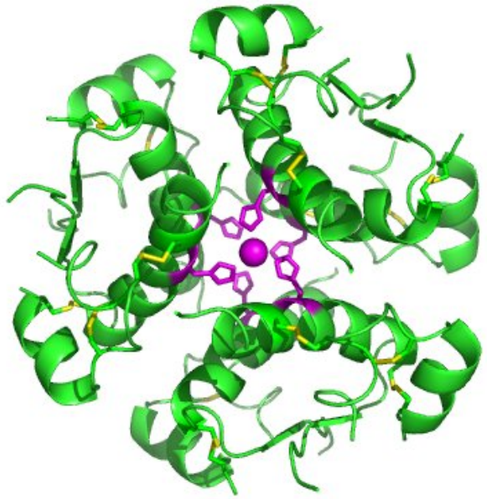
Category	Class	A1C decrease	Drugs	Relative Cost
Sensitizer	Biguanides	1.0-2.0%	metformin	$ (generic)
	TZDs	0.5-1.4%	pioglitazone rosiglitazone	$$$$
Secretagogue	Sulfonylureas	1.0-2.0%	(various)	$ (generic)
	Metaglitinides	0.5-1.5%	repaglinide netaglinide	$$$
	GLP-1 analog	0.5-1.5%	exenatide liraglutide	$$$$
	DPP4 inhibitor	0.5-0.8%	sitagliptin saxagliptin linagliptin	$$$$
Others	α-glucosidase inhibitor	0.5-0.8%	miglitol acarbose	$$
	Amylin analog	0.5-1.0%	pramlintide	$$
	Dopamine agonist	~0.5%	bromocriptine	$$
	Bile acid sequestrant	~0.5%	colesevelam	$$
	SGLT2 Inhibitor	~0.5-1.0%	canagliflozin dapagliflozin	$$$$

Insulin / Analogs

- Most effective at glycemic control
  - Expected A1C reduction = 1.5-3.5%
    - able to lower any A1C to near goal
- Advantages
  - Available in a range of onset/duration
- Disadvantages
  - Requires subcutaneous injection
  - Risk of hypoglycemia

Insulin / Analogs

- Rapid-Acting
  - Glulisine
    - *Apidra*
  - Lispro
    - *Humalog*
  - Aspart
    - *NovoLog*
  - Inhaled
    - *Afrezza*
- Short-Acting
  - Regular Human Insulin
    - *Humulin R*
    - *Novolin R*



Created by Isaac Yonemoto.; 2006. https://commons.wikimedia.org/wiki/File:InsulinHexamer.jpg. Accessed June 30, 2016.

- Intermediate-Acting
  - NPH Human Insulin (Neutral Protamine Hagedorn)
    - *Humulin N*
    - *Novolin N, Novolin NPH*
    - *Isophane insulin*
- Long-Acting
  - Glargine
    - *Lantus (U100)*, ***Basaglar***
    - *Toujeo (U300) – pen only*
  - Detemir
    - *Levemir*
- Ultra-Long-Acting
  - Degludec (FDA-approved Oct 2015)
    - *Tresiba (U100 & U200) – pen only*

Inhaled Insulin

- New in 2016:
  - Doing poorly in market
  - (*Sanofi* dropped marketing, *MannKind* continuing)

- Human insulin
  - 4 mg (blue) &
  - 8 mg (green) cartridges
  - Rapid acting
    - Equivalent to lispro
  - Used with Basal insulin
  - Pregnancy class C

- Adverse effects
  - Hypoglycemia (!)
  - Cough (25%)
- Recommend spirometry in all patients
  - Baseline, after 6 months, & annually
    - Small decline in FEV1 in normal patients
  - Not recommended in smokers
  - Contraindicated in COPD/Chronic Lung Disease (asthma)
    - Bronchospasm risk

Insulin / Analogs

Class	Preparation	Onset	Peak	Duration
Rapid	Lispro	5 – 15 minutes	1 – 2 hours	4 – 5 hours
	Aspart	5 – 15 minutes	1 – 2 hours	4 – 5 hours
	Glulisine	5 – 15 minutes	1 – 2 hours	4 – 5 hours
	Inhaled	(comparable to lispro)	~1 – 2 hours	~2.5 hours
Short	Regular Human	30 – 60 minutes	2 – 4 hours	8 – 10 hours
Intermediate	NPH	1 – 2 hours	4 – 8 hours	10 – 20 hours
Long	Detemir	1 – 2 hours	Flat	12 – 20 hours
	Glargine	1 – 2 hours	Flat	20 – 24 hours
Ultra-long	Degludec	30 – 90 minutes	Flat	> 24 hours (half-life 25 hours)

Adapted from Ripsin CM, Kang H, Urban RJ. Management of blood glucose in type 2 diabetes mellitus. *Am Fam Physician*. 2009;79(1):29-36.

Glycemic Targets

- American Diabetes Association (ADA)
  - A1C < 7.0%
  - Preprandial
    - 80-130 mg/dL
  - Peak postprandial
    - < 180 mg/dL
    - (1-2 hours after starting meal)
- A1C testing
  - Twice a year in those meeting goals (E)
  - Quarterly in those not meeting goals (or with change in therapy) (E)
  - Use A1C point-of-care testing for timely changes (E)

Standards of Medical Care in Diabetes—2016 Abridged for Primary Care Providers. *Clinical Diabetes*. 2016;34(1):3-21. doi:10.2337/diaclin.34.1.3.

Pre-Assessment Question

Mr. H is an 84-year-old male with long-standing DM type 2, h/o MI, and s/p CABG, with stage 2 CKD. He now returns with an A1C of 6.8%. He reports no significant symptoms but has had occasional AM fasting blood sugars down to mid-60s. On other mornings he notes blood sugars as high as 182 mg/dL. You take his blood sugar and it is currently 58 mg/dL.

5. What is the best approach to the continued care of this patient?
   - A. No change to his medications, because his A1C is within the goal range, thereby reducing his risk of further cardiovascular complications.
   - B. Change his medication regimen to prevent hypoglycemia, considering a new A1C goal possibly as high as 8.0%.
   - C. Increase his medications to achieve an A1C goal of 6.5% in order to further reduce his risk of cardiovascular disease, because it is the diabetic complication associated with greatest mortality.
   - D. Keep his A1C goal at 7.0% but consider a change to insulin to better control his glycemic swings.
   - E. Ask him to perform fingerstick blood glucose checks 3 or 4 times daily to guide any medication changes.

A1C Goals – nonpregnant adults

- <7% most (A)
  - Reduces microvascular complications
- <6.5% if no hypoglycemia or adverse events (C)
  - Short duration of DM
  - Type 2 DM on lifestyle or metformin only
  - Long life expectancy
  - No significant CVD

- <8% or higher (B)
  - H/O severe hypoglycemia
  - Limited life expectancy
  - Advanced micro-macrovascular complications
  - Extensive comorbid conditions
  - Long-standing diabetes / difficult to control

Standards of Medical Care in Diabetes—2016 Abridged for Primary Care Providers. *Clinical Diabetes*. 2016;34(1):3-21. doi:10.2337/diaclin.34.1.3.

Hypoglycemia

- Ask at-risk patients about hypoglycemia (symptomatic or asymptomatic) at each encounter. (C)
- Treat hypoglycemia ("Rule of 15s") (E)
  - Glucose 15-20 g preferred
    - Any carbohydrate acceptable
  - Check blood sugar after 15 minutes
  - Repeat glucose 15-20 g if hypoglycemia persists
  - Once blood sugar normal, consume meal or snack
- Prescribe glucagon for those at risk of severe hypoglycemia. Instruct family members and caregivers in administration. (E)
- In those with severe hypoglycemia or unawareness:
  - Reevaluate treatment (E)
  - If insulin treated, raise glycemic goal for several weeks (to partially reverse hypoglycemia unawareness) and reduce risk of further episodes (A)
- If low/declining cognition, increased hypoglycemia vigilance by clinician, patient and caregivers (B)

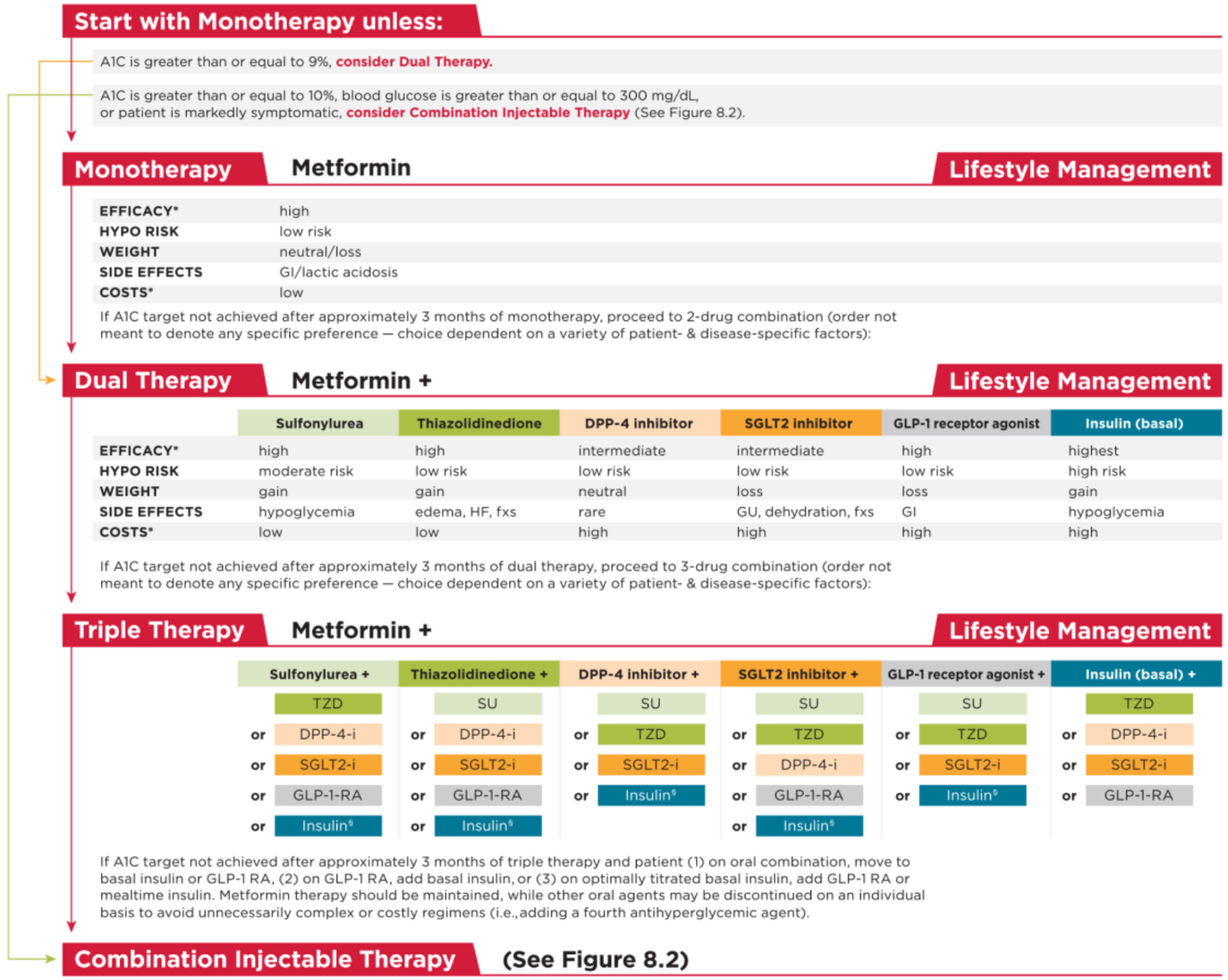
Standards of Medical Care in Diabetes—2017 Abridged for Primary Care Providers. *Clinical Diabetes*. 2017;35(1):5-26. doi:10.2337/cd16-0067.

Pharmacologic Therapy for Type 2

- Monotherapy
  - Metformin is preferred initial agent (A) (remember B12!)
  - Consider insulin in newly diagnosed
    - Symptomatic and/or markedly elevated glucose / A1C (E)
- Dual Therapy
  - A1C not at goal after 3 months on (non-insulin) monotherapy
    - Add second oral, GLP-1 RA, or basal insulin (A)
- Use patient-centered approach to choice of agent. (E)
  - Consider efficacy, cost, side effects, weight, comorbidities, hypoglycemia risk, patient preference
- For those not achieving glycemic goals **Insulin therapy should not be delayed** (B)
- w/ long-standing suboptimally controlled type 2 DM and established ASCVD, consider empagliflozin or liraglutide. (B)

Standards of Medical Care in Diabetes—2017 Abridged for Primary Care Providers. *Clinical Diabetes*. 2017;35(1):5-26. doi:10.2337/cd16-0067.

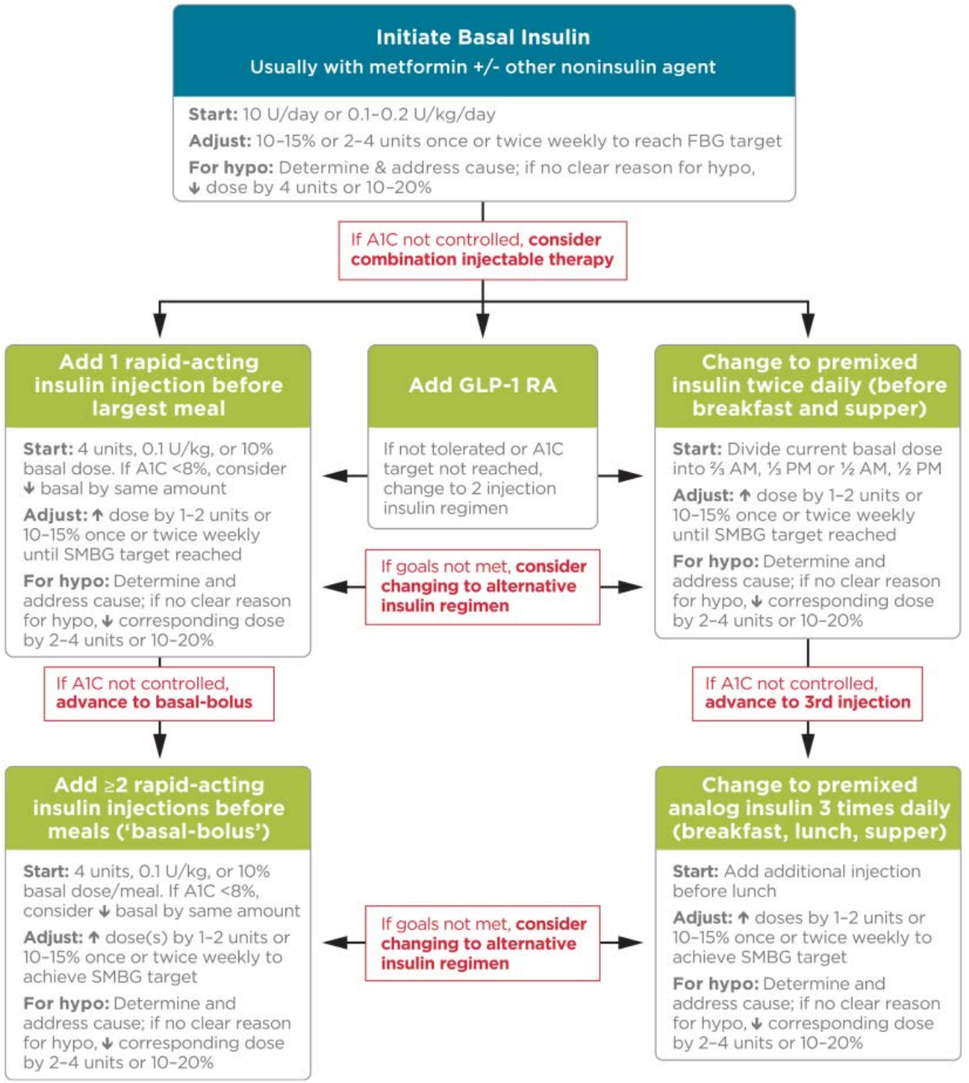
Antihyperglycemic Therapy in T2DM



American Diabetes Association Standards of Medical Care in Diabetes. Approaches to glycemic treatment. Diabetes Care 2017; 40 (Suppl. 1): S64-S74

American Diabetes Association.

Combination Injectable Therapy in T2DM



American Diabetes Association Standards of Medical Care in Diabetes. Approaches to glycemic treatment. Diabetes Care 2017; 40 (Suppl. 1): S64-S74

American Diabetes Association.

Pharmacologic Therapy for Type 2

- Monotherapy
  - Metformin
    - *Consider using eGFR ≥ 30 mL/min
  - If contraindicated/not tolerated, then use 2nd line:
    - Avoid Sulfonylureas
      - hypoglycemia risk
    - DPP-4 inhibitors preferable
- Combinations to avoid:
  - DPP-4-i + GLP-1-RA
    - Affect same pathway
  - Multiple-dose insulin + Sulfonylurea (any Insulin Secretagogues)
    - Need implies significant β-cell dysfunction

Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015;38(1):140-149. doi:10.2337/dc14-2441.

DM Goals in Elderly

Health	Life Expectancy	A1C goal	Fasting or preprandial goal (mg/dL)	Bedtime glucose goal (mg/dL)	Blood Pressure goal (mm/Hg)	Lipid Treatment (unless contraindicated/ not tolerated)
Healthy (few chronic conditions, good cognition)	Longer	<7.5%	90-130	90-150	<140/90	Statin
Intermediate (multiple chronic conditions, mild-moderate cognitive impairment)	Intermediate	<8.0%	90-150	100-180	<140/90	Statin
Poor (long-term care, end-stage illness, moderate to severe cognitive impairment)	Limited	<8.5%	100-180	110-200	<150/90	Consider benefit (secondary prevention)

Adapted from Standards of Medical Care in Diabetes—2016 Abridged for Primary Care Providers. *Clinical Diabetes*. 2016;34(1):3-21. doi:10.2337/diaclin.34.1.3.

Pre-Assessment Question

Mr. B is an obese white male with a BMI of 47 kg/m^2. He has had significant difficulty controlling his blood sugar despite triple oral therapy with metformin, exenatide (a GLP-1) and empagliflozin (an SGLT-2i).

6. The current ADA guidelines recommend consideration of which of the following treatments?

A. Change his GLP-1 agonist to liraglutide and increase dose to stimulate weight loss.
B. Consider bariatric surgery such as a Roux-en-Y gastric bypass.
C. Add an ultra-long-acting insulin to decrease appetite and cause weight loss.
D. Consider a DPP-4i since it should also stimulate weight loss.
E. Add acarbose to cause adverse effects of diarrhea and flatulence.

Obesity Management

- Calculate/document BMI at each visit (B)
- In those willing to lose weight:
  - Prescribe diet, physical activity, behavioral therapy to achieve 5% weight loss (A)
    - Use high-intensity (≥16 sessions in 6 months) interventions, focused on 500-750 kcal/day deficit (A)
    - Diets w/ same caloric restriction (different protein, carbohydrate, fat content) are equally effective (A)
    - If meeting short-term goals, refer to long-term (>1 year) comprehensive weight management programs (A)
  - In selected patients, consider >5% weight loss w/ short-term (3 month) very-low calorie diets (< 800 kcal/day) with trained providers and close medical monitoring (B)
- Pharmacotherapy
  - Consider effect on weight when choosing glucose-lowering meds (E)
  - Minimize meds associated w/ weight gain for comorbid conditions (E)
  - Consider weight loss medications for selected type 2 patients w/ BMI ≥ 27 kg/m^2 (A)
    - Discontinue meds if < 5% weight loss after 3 months or not tolerated (A)

Standards of Medical Care in Diabetes—2017 Abridged for Primary Care Providers. *Clinical Diabetes*. 2017;35(1):5-26. doi:10.2337/cd16-0067.

Metabolic Surgery

- **Recommended** to treat type 2 DM in appropriate surgical candidates (A)
  - w/ BMI ≥ 40 kg/m^2 regardless of glycemic control
  - adults w/ BMI = 35-39 when inadequately controlled despite lifestyle and optimal medical therapy
- **Considered** w/ BMI 30-34.9 if inadequately controlled despite optimal medical control by oral or injectable medications (B)

- Should be performed in high-volume centers (C)
- Metabolic surgery patients:
  - Require long-term lifestyle support (C)
  - Before surgery should receive comprehensive mental health assessment (B)
  - Surgery postponed w/ h/o alcohol/substance abuse, significant depression, suicidal ideation, other mental health conditions until addressed (E)
  - After surgery, assess need for ongoing mental health services (C)

Standards of Medical Care in Diabetes—2017 Abridged for Primary Care Providers. *Clinical Diabetes*. 2017;35(1):5-26. doi:10.2337/cd16-0067.

Pre-Assessment Question

7. Mr. H. is a 67-year-old Middle Eastern male who was diagnosed with Diabetes several years ago and has had his medication titrated to where he is currently controlled on extended-release glipizide 20 mg. While he usually sees your partner, he came to urgently to see you last week with complaints of episodes of feeling lightheaded, dizzy and clammy. He took his blood sugar when this happened and found it to be 58 mg/dL. He remembers having symptoms like this last summer, but they were not so severe. He does not remember any such episodes last fall or winter.

Pre-Assessment Question (continued)

On further questioning, it turns out that Mr. H. has been fasting during daylight hours for the month Ramadan during these times. He has continued to take his glipizide in the morning.

7. Which simple intervention may help eliminate his hypoglycemic episodes, yet maintain control?
   A. Stop glipizide until Ramadan ends.
   B. Change to a glinide medication taken twice daily.
   C. Forbid Mr. H from participating in the Ramadan fast.
   D. Take glipizide with the evening meal.

Treatment during fasting

- Ramadan
  - Holy month of fasting practiced by most Muslims
  - ~ 30 days, fasting during daylight hours.
  - Two daily meals
    - Suhur – meal before dawn
    - Iftar – meal after sunset
  - Ill individuals are exempted from fasting
    - 79% type 2 diabetics fast anyway

Hui E, Bravis V, Hassanein M, et al. Management of people with diabetes wanting to fast during Ramadan. *BMJ*. 2010;340(jun22 2):c3053–c3053.

Treatment during fasting

- High Risk
    - Severe/recurrent hypoglycemia/unawareness
    - Poor glycemic control
    - Ketoacidosis/hyperosmolar coma in last 3 months
    - Acute illness, Intense physical labor
    - Pregnant
    - Advanced macrovascular complications, renal disease, dialysis, cognitive dysfunction
- Moderate Risk
    - Well controlled; Treated with short-acting insulin secretagogues, sulfonylureas, insulin +/- oral
- Low Risk
    - Well controlled/healthy; Treated with diet alone, metformin, DPP-4 inhibitor, TZD

Hui E, Bravis V, Hassanein M, et al. Management of people with diabetes wanting to fast during Ramadan. *BMJ*. 2010;340(jun22 2):c3053–c3053.

Ramadan-Medication Adjustment

- Diet-controlled
  - Split calories over two meals
  - Complex carbs (pre-dawn)
  - Simple carbs (sunset)
  - Avoid high fat/sugar foods
  - Adequate fluid intake non-fasting hours
- Orals:
  - DPP4i, ‘glinides,’ TZD at mealtime without adjustment
  - Metformin
    - 1/3 dose pre-dawn
    - 2/3 dose sunset
    - - or – ER at sunset
  - Sulfonylurea
    - Once daily at sunset
    - Twice daily, reduce pre-dawn

Hui E, Bravis V, Hassanein M, et al. Management of people with diabetes wanting to fast during Ramadan. *BMJ*. 2010;340(jun22 2):c3053–c3053.

Post-Assessment Question

1. Prediabetes is defined as a fasting glucose in the range of 100-125 mg/dL, referred to as Impaired Fasting Glucose (IFG) or an A1C in the range of 5.7% to 6.4%, among other criteria.

   Between these two measures, impaired fasting glucose is a better predictor of subsequent diabetes and cardiovascular disease than is a baseline A1C in the prediabetes range.

   A. True
   B. False

Post-Assessment Question

2. Which of the following medication classes can, on average, achieve the greatest decrease in A1C alone?

A. A thiazolidinedione (e.g. pioglitazone)
B. An SGLT-2i (e.g. canagliflozin)
C. A biguanide (e.g. metformin)
D. A DPP-4i (e.g. sitagliptin)
E. A meglitnide (e.g. repaglinide)

Case #1

Mrs. M is a 66-year-old female with a long-standing diagnosis of type 2 diabetes. She has used metformin at a dose of 1000 mg twice daily for 8 years, adding insulin glargine to her regimen 3 years ago. Under your direction, she has titrated the insulin glargine to 40 units at bedtime daily. You have followed Mrs. M closely since her renal function began to worsen 2 years ago. On her recent lab work, you noticed that she now has CKD 3a since her eGFR is now at 40.

Post-Assessment Question – Case #1

3. What is the most immediate medication course of action given the finding of worsening renal function in this patient?

A. Stop metformin immediately, adding an SGLT-2 inhibitor to compensate.
B. Decrease her insulin glargine to compensate for lack of renal clearance.
C. Add a DPP-4 inhibitor to improve renal function.
D. Continue metformin at current dose, continuing to closely monitor renal function.
E. Change insulin glargine to rapid-acting insulin three times daily.

Case #2 (Continued)

Mrs. M has remained on metformin and insulin glargine for several more months, with no further significant reduction in her renal function. She continues to have good AM fasting blood sugars averaging around 110 mg/dL. Despite this, her A1c is above goal at 8.2%, and she has noticed that her fasting blood sugars before lunch and dinner are now much higher, averaging 190 mg/dL. She would like to continue to maintain good blood sugar control.

Post-Assessment Question – Case #2

4. What is the best medication change at this time?

A. Increase her insulin glargine by at least 50% to better control pre-meal blood sugar.
B. Add a GLP-1 (daily or weekly) to achieve a better blood sugar control at least risk of hypoglycemia.
C. Add pre-meal insulin to reduce overall risk of hypoglycemia.
D. Stop metformin because it is likely causing hyperglycemia as a response to metabolic acidosis.
E. Change insulin glargine to rapid-acting insulin three times daily.

Post-Assessment Question

Mr. H is an 84-year-old male with long-standing DM type 2, h/o MI, and s/p CABG, with stage 2 CKD. He now returns with an A1C of 6.8%. He reports no significant symptoms but has had occasional AM fasting blood sugars down to mid-60s. On other mornings he notes blood sugars as high as 182 mg/dL. You take his blood sugar and it is currently 58 mg/dL.

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Questions

Contact Information

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- Twitter: @pziemkowski

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