American Diabetes Association®

Standards of Medical Care in Diabetes — 2016

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November 4, 2016

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Presenter Disclosure Information

In compliance with the accrediting board policies, the American Diabetes Association requires the following disclosure to the participants:

Fawn M. Wolf, MD

Disclosed no conflict of interest

Clinical Practice Recommendations Evidence Grading System

A	• Clear evidence from adequately-powered, well-conducted, generalizable RCTs, including evidence from a multicenter trial or meta-analysis that incorporated quality ratings in the analysis; • Compelling nonexperimental evidence; • Supportive evidence from adequately-powered, well-conducted RCTs.
B	• Supportive evidence from a well-conducted cohort studies • Supportive evidence from a well-conducted case-control study
C	• Supportive evidence from poorly controlled or uncontrolled studies or evidence from observational studies with high potential for bias • Evidence from case series or case reports • Conflicting evidence with the weight of evidence supporting the recommendation
E	• Expert consensus or clinical experience

American Diabetes Association

American Diabetes Association Standards of Medical Care in Diabetes. Introduction. *Diabetes Care* 2016; 39 (Suppl. 1): S1-S2

2. Classification and Diagnosis of Diabetes

Criteria for the Diagnosis of Diabetes

Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L)

OR

2-h plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT

OR

A1C ≥6.5%

OR

Random plasma glucose ≥200 mg/dL (11.1 mmol/L)

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American Diabetes Association Standards of Medical Care in Diabetes. Classification and diagnosis of diabetes. *Diabetes Care* 2016; 39 (Suppl. 1): S13-S22

A1C ≥6.5% *

- Performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay – www.ngsp.org
- POC testing not recommended
- Greater convenience, preanalytical stability, and less day-to-day perturbations than FPG and OGTT
- Consider cost, age, race / ethnicity, anemia, etc.

American Diabetes Association Standards of Medical Care in Diabetes. Classification and diagnosis of diabetes. *Diabetes Care* 2016; 39 (Suppl. 1): S13-S22

Prediabetes*

FPG 100–125 mg/dL (5.6–6.9 mmol/L): IFG

OR

2-h plasma glucose 140–199 mg/dL (7.8–11.0 mmol/L): IGT

OR

A1C 5.7–6.4%

*** For all three tests, risk is continuous, extending below the lower limit of a range and becoming disproportionately greater at higher ends of the range.**

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American Diabetes Association Standards of Medical Care in Diabetes. Classification and diagnosis of diabetes. *Diabetes Care* 2016; 39 (Suppl. 1): S13-S22

Recommendation: Screening for Type 1 Diabetes

- Blood glucose rather than A1C should be used to dx type 1 diabetes in symptomatic individuals. **E**
- Inform relatives of patients with T1D of the opportunity to be tested for type 1 diabetes risk, but only in the setting of a clinical research study. **E**

www.DiabetesTrialNet.org

American Diabetes Association Standards of Medical Care in Diabetes. Classification and diagnosis of diabetes. *Diabetes Care* 2016; 39 (Suppl. 1): S13-S22

Recommendations: Screening for Type 2 Diabetes

- Consider testing in asymptomatic adults of any age with BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans who have 1 or more add'l dm risk factors. **B**
- For all patients, testing should begin at age 45 years. **B**
- If tests are normal, repeat testing carried out at a minimum of 3-year intervals is reasonable. **C**

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American Diabetes Association Standards of Medical Care in Diabetes. Classification and diagnosis of diabetes. *Diabetes Care* 2016; 39 (Suppl. 1): S13-S22

Recommendations: Detection and Diagnosis of GDM

- Test for undiagnosed T2DM at the 1st prenatal visit in those with risk factors. B
- Test for GDM at 24–28 weeks of gestation in women not previously known to have diabetes. A
- Screen women with GDM for persistent diabetes at 6–12 weeks postpartum, using the OGTT. E

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American Diabetes Association Standards of Medical Care in Diabetes. Classification and diagnosis of diabetes. *Diabetes Care* 2016; 39 (Suppl. 1): S13-S22

Recommendations: Detection and Diagnosis of GDM (2)

- Women with GDM history should have lifelong screening for development of diabetes or prediabetes at least every 3 years. B
- Women with GDM history found to have prediabetes should receive lifestyle interventions or metformin to prevent diabetes. A

American Diabetes Association Standards of Medical Care in Diabetes. Classification and diagnosis of diabetes. *Diabetes Care* 2016; 39 (Suppl. 1): S13-S22

4. Prevention or Delay of Type 2 Diabetes

Recommendations: Prevention or Delay of T2DM

- Patients with prediabetes should be referred to an intensive diet and physical activity behavioral counseling program adhering to the tenets of the DPP targeting a loss of 7% of body weight, and should increase their moderate physical activity to at least 150 min/week. A
- Offer follow-up counseling and maintenance programs for long-term success in preventing diabetes. B

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American Diabetes Association Standards of Medical Care in Diabetes. Prevention or delay of type 2 diabetes. *Diabetes Care* 2016; 39 (Suppl. 1): S36-S38

Recommendations: Prevention or Delay of T2DM (2)

- Based on cost-effectiveness of diabetes prevention, such programs should be covered by third-party payers. **B**
- Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially for those with BMI >35 kg/m^2, aged < 60 years, and women with prior gestational diabetes (GDM). **A**

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American Diabetes Association Standards of Medical Care in Diabetes. Prevention or delay of type 2 diabetes. *Diabetes Care* 2016; 39 (Suppl. 1): S36-S38

Recommendations: Prevention or Delay of T2DM (3)

- Monitor at least annually for the development of diabetes in those with prediabetes. E
- Screening for and treatment of modifiable risk factors for CVD is suggested. B

American Diabetes Association Standards of Medical Care in Diabetes. Prevention or delay of type 2 diabetes. *Diabetes Care* 2016; 39 (Suppl. 1): S36-S38

5. Glycemic Targets

Diabetes Care: Glycemic Control

- **Two primary techniques available for health providers and patients to assess effectiveness of management plan on glycemic control**
  1. **Patient self-monitoring of blood glucose (SMBG)**
  2. **A1C**
- **CGM or interstitial glucose may be a useful adjunct to SMBG in selected patients.**

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American Diabetes Association Standards of Medical Care in Diabetes. Glycemic targets. *Diabetes Care* 2016; 39 (Suppl. 1): S39-S46

Recommendations: Glucose Monitoring (2)

- **Patients on multiple-dose insulin (MDI) or insulin pump therapy should do SMBG B**
  - **Prior to meals and snacks**
  - **At bedtime**
  - **Prior to exercise**
  - **When they suspect low blood glucose**
  - **After treating low blood glucose until they are normoglycemic**
  - **Prior to critical tasks such as driving**
  - **Possibly also post-prandially**

American Diabetes Association Standards of Medical Care in Diabetes. Glycemic targets. *Diabetes Care* 2016; 39 (Suppl. 1): S39-S46

Recommendations: Glucose Monitoring (3)

- When used properly, CGM in conjunction with intensive insulin regimens is a useful tool to lower A1C in selected adults (aged ≥ 25 years) with type 1 diabetes. A
- Although the evidence for A1C lowering is less strong in children, teens, and younger adults, CGM may be helpful in these groups. Success correlates with adherence to ongoing use of the device. B
- CGM may be a supplemental tool to SMBG in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes. C

American Diabetes Association Standards of Medical Care in Diabetes. Glycemic targets. *Diabetes Care* 2016; 39 (Suppl. 1): S39-S46

Recommendations: Glucose Monitoring (4)

- Given variable adherence to CGM, assess individual readiness for continuing use of CGM prior to prescribing. E
- When prescribing CGM, robust diabetes education, training, and support are required for optimal CGM implementation and ongoing use. E

American Diabetes Association Standards of Medical Care in Diabetes. Glycemic targets. *Diabetes Care* 2016; 39 (Suppl. 1): S39-S46

Mean Glucose Levels for Specified A1C Levels

	Mean Glucose					
	Mean Plasma Glucose*		Fasting	Premeal	Postmeal	Bedtime
A1C%	mg/dL	mmol/L	mg/dL	mg/dL	mg/dL	mg/dL
6	126	7.0				
<6.5			122	118	144	136
6.5-6.99			142	139	164	153
7	154	8.6				
7.0-7.49			152	152	176	177
7.5-7.99			167	155	189	175
8	183	10.2				
8-8.5			178	179	206	222
9	212	11.8	professional.diabetes.org/eAG			
10	240	13.4				
11	269	14.9				
12	298	16.5				

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American Diabetes Association Standards of Medical Care in Diabetes. Glycemic targets. *Diabetes Care* 2016; 39 (Suppl. 1): S39-S46

Recommendations: Glycemic Goals in Adults

- Lowering A1C to <7% has been shown to reduce microvascular complications and, if implemented soon after the diagnosis of diabetes, is associated with long-term reduction in macrovascular disease. B
- Consider more stringent goals (e.g. <6.5%) for select patients if achievable without significant hypos or other adverse effects. C
- Consider less stringent goals (e.g. <8%) for patients with a hx of severe hypoglycemia, limited life expectancy, or other conditions that make <7% difficult to attain. B

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American Diabetes Association Standards of Medical Care in Diabetes. Glycemic targets. *Diabetes Care* 2016; 39 (Suppl. 1): S39-S46

A1C and CVD Outcomes

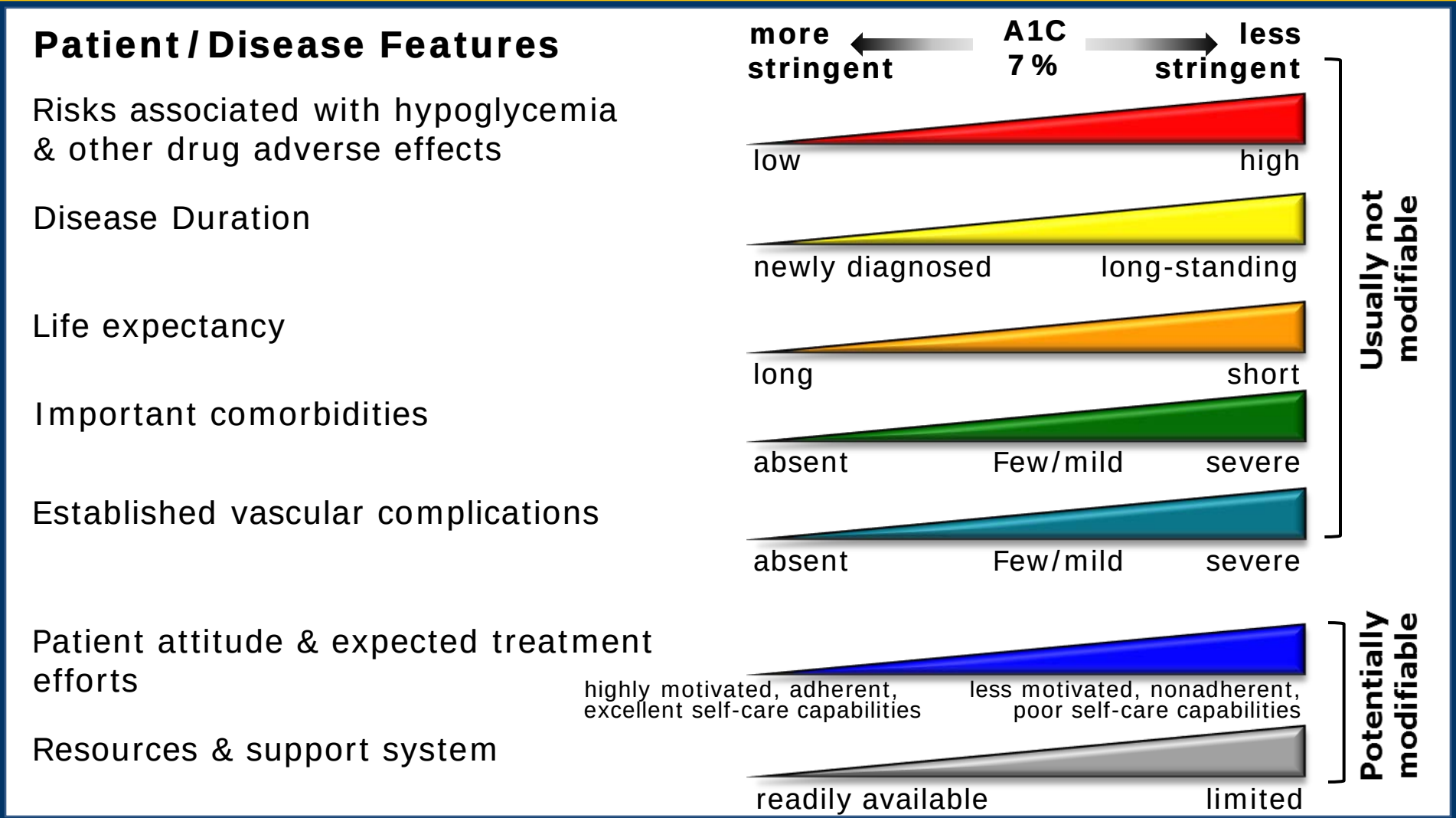
- **DCCT: Lower risk of CVD events with intensive control**
- **EDIC: 57% reduction in risk of nonfatal MI, stroke, or CVD death**
- **Benefit of intensive glycemic control persists for decades and is associated with a modest reduction in all-cause mortality.**
- **ACCORD, ADVANCE, VADT suggested no significant reduction in CVD outcomes with intensive glycemic control.**

Care.DiabetesJournals.org

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American Diabetes Association Standards of Medical Care in Diabetes. Glycemic targets. *Diabetes Care* 2016; 39 (Suppl. 1): S39-S46

Approach to the Management of Hyperglycemia



American Diabetes Association Standards of Medical Care in Diabetes. Glycemic targets. *Diabetes Care* 2016; 39 (Suppl. 1): S39-S46

6. Obesity Management for the Treatment of Type 2 Diabetes

Recommendations: Diet, physical activity & behavioral therapy

- Diet, physical activity & behavioral therapy designed to achieve 5% weight loss should be prescribed for overweight & obese patients with T2DM ready to achieve weight loss. A
- Interventions should be high-intensity (≥16 sessions in 6 months) and focus on diet, physical activity & behavioral strategies to achieve a 500 - 750 kcal/day energy deficit. A

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American Diabetes Association Standards of Medical Care in Diabetes. Obesity management for the treatment of type 2 diabetes. *Diabetes Care* 2016; 39 (Suppl. 1): S47-S51

Recommendations: Diet, physical activity & behavioral therapy

- Diets that provide the same caloric restriction but differ in protein, carbohydrate, and fat content are equally effective in achieving weight loss. A
- Patients who achieve short-term weight loss goals should be prescribed long-term maintenance programs. A

American Diabetes Association Standards of Medical Care in Diabetes. Obesity management for the treatment of type 2 diabetes. *Diabetes Care* 2016; 39 (Suppl. 1): S47-S51

Recommendations: Pharmacotherapy

- If patient response to weight loss medications <5% after 3 months or there are safety or tolerability issues at any time, discontinue medication and consider alternative medications or treatment approaches. A

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American Diabetes Association Standards of Medical Care in Diabetes. Obesity management for the treatment of type 2 diabetes. *Diabetes Care* 2016; 39 (Suppl. 1): S47-S51

Bariatric Surgery

- Guidelines support gastric banding, gastrectomy, and bypass as effective treatments for overweight T2DM patients.
- In 72% of patients, bariatric surgery helped achieve near- or complete normalization of glycemia 2 yrs post-surgery.
- In one meta-analysis, gastric banding resulted in less weight loss than gastrectomy or Roux-en-Y.

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American Diabetes Association Standards of Medical Care in Diabetes. Obesity management for the treatment of type 2 diabetes. *Diabetes Care* 2016; 39 (Suppl. 1): S47-S51

7. Approaches to Glycemic Treatment

Recommendations: Pharmacological Therapy For Type 1 Diabetes

- Most people with T1DM should be treated with multiple dose insulin (MDI) injections (3–4 injections /day of basal & prandial insulin) or continuous subcutaneous insulin infusion (CSII). **A**
- Individuals who have been successfully using CSII should have continued access after they turn 65 years old. **E**

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American Diabetes Association Standards of Medical Care in Diabetes. Approaches to glycemic treatment. *Diabetes Care* 2016; 39 (Suppl. 1): S52-S59

8. Cardiovascular Disease and Risk Management

Blood Pressure Control & T2DM

Action to Control Cardiovascular Risk in Diabetes (ACCORD):

- Does SBP <120 provide better cardiovascular protection than SBP 130-140? **No.**

ADVANCE-BP:

- Significant risk reduction

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American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. *Diabetes Care* 2016; 39 (Suppl. 1): S60-S71

Recommendations: Hypertension / Blood Pressure Control (2)

Systolic Targets:

- People with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg. **A**
- Lower systolic targets, such as <130 mmHg, may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden. **C**

American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. *Diabetes Care* 2016; 39 (Suppl. 1): S60-S71

Recommendations: Hypertension / Blood Pressure Control (3)

Diastolic Targets:

- Patients with diabetes should be treated to a diastolic blood pressure <90 mmHg. **A**
- Lower diastolic targets, such as <80 mmHg, may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden. **B**

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American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. *Diabetes Care* 2016; 39 (Suppl. 1): S60-S71

Recommendations: Lipid Management

- In adults not taking statins, a screening lipid profile is reasonable **(E)**:
  - At diabetes diagnosis
  - At the initial medical evaluation
  - And every 5 years, or more frequently if indicated
- Obtain a lipid profile at initiation of statin therapy, and periodically thereafter. **E**

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American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. *Diabetes Care* 2016; 39 (Suppl. 1): S60-S71

Recommendations for Statin Treatment in People with Diabetes

Age	Risk Factors	Statin Intensity*
<40 years	None	None
	ASCVD risk factor(s)**	Moderate or high
	ASCVD	High
40–75 years	None	Moderate
	ASCVD risk factors	High
	ACS & LDL >50 who can't tolerate high dose statin	Moderate + ezetimibe
>75 years	None	Moderate
	ASCVD risk factors	Moderate or high
	ASCVD	High
	ACS & LDL >50 who can't tolerate high dose statin	Moderate + ezetimibe

* In addition to lifestyle therapy. ** ASCVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, overweight and obesity, and family history of premature ASCVD.

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American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. *Diabetes Care* 2016; 39 (Suppl. 1): S60-S71

Recommendations: Lipid Management (4)

- In clinical practice, providers may need to adjust intensity of statin therapy based on individual patient response to medication (e.g., side effects, tolerability, LDL cholesterol levels). E
- Ezetimibe + moderate intensity statin therapy provides add'l CV benefit over moderate intensity statin therapy alone; consider for patients with a recent acute coronary syndrome w/ LDL ≥ 50mg/dL or in patients who can't tolerate high-intensity statin therapy. A

American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. *Diabetes Care* 2016; 39 (Suppl. 1): S60-S71

Recommendations: Lipid Management (5)

- Combination therapy (statin/fibrate) doesn't improve ASCVD outcomes and is generally not recommended A. Consider therapy with statin and fenofibrate for men with *both* trigs ≥204 mg/dL (2.3 mmol/L) and HDL ≤34 mg/dL (0.9 mmol/L). B
- Combination therapy (statin/niacin) hasn't demonstrated additional CV benefit over statins alone, may raise risk of stroke & is not generally recommended. A
- Statin therapy is contraindicated in pregnancy. B

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American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. *Diabetes Care* 2016; 39 (Suppl. 1): S60-S71

High- and Moderate-Intensity Statin Therapy*

High Intensity Statin Therapy	Moderate-Intensity Statin Therapy
Lowers LDL by ≥50%	Lowers LDL by 30 - <50%
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg
Rosuvastatin 20-40 mg	Rosuvastatin 5-10 mg
	Simvastatin 20-40 mg
	Pravastatin 40-80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 2-4 mg

* Once-daily dosing

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American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. *Diabetes Care* 2016; 39 (Suppl. 1): S60-S71

Recommendations: Antiplatelet Agents

Consider aspirin therapy (75–162 mg/day) C

- **As a primary prevention strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk (10-year risk >10%)**
- **Includes most men or women with diabetes age ≥50 years who have at least one additional major risk factor, including:**
  - **Family history of premature ASCVD**
  - **Hypertension**
  - **Smoking**
  - **Dyslipidemia**
  - **Albuminuria**

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American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. *Diabetes Care* 2016; 39 (Suppl. 1): S60-S71

Recommendations: Antiplatelet Agents (2)

- **Aspirin is not recommended for ASCVD prevention for adults with DM at low ASCVD risk, since potential adverse effects from bleeding likely offset potential benefits. C**
  - **Low risk: 10-year CVD risk <5%, such as in men or women with diabetes aged <50 years with no major additional ASCVD risk factors)**
- **In patients with diabetes <50 years of age with multiple other risk factors (e.g., 10-year risk 5–10%), clinical judgment is required. E**

American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. *Diabetes Care* 2016; 39 (Suppl. 1): S60-S71

9. Microvascular Complications and Foot Care

Recommendations: Diabetic Kidney Disease

Treatment (5)

- An ACE inhibitor or ARB isn't recommended for primary prevention of diabetic kidney disease in patients with diabetes with normal BP, normal UACR (<30 mg/g) & normal eGFR. **B**
- When eGFR is <60, evaluate and manage potential complications of CKD. **E**

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American Diabetes Association Standards of Medical Care in Diabetes. Microvascular complications and foot care. *Diabetes Care* 2016; 39 (Suppl. 1): S72-S80

Recommendations: Diabetic Kidney Disease

Treatment (6)

- If patients have eGFR <30, refer for evaluation for renal replacement treatment. A
- Promptly refer to a physician experienced in the care of DKD for: B
  - Uncertainty about the etiology of disease
  - Difficult management issues
  - Rapidly progressing kidney disease.

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American Diabetes Association Standards of Medical Care in Diabetes. Microvascular complications and foot care. *Diabetes Care* 2016; 39 (Suppl. 1): S72-S80

Recommendations: Diabetic Retinopathy (6)

Treatment:

- Promptly refer patients with macular edema, severe NPDR, or any PDR to an ophthalmologist knowledgeable & experienced in management, treatment of diabetic retinopathy. A
- Laser photocoagulation therapy is indicated to reduce the risk of vision loss in patients with high-risk PDR and, in some cases, severe NPDR. A

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American Diabetes Association Standards of Medical Care in Diabetes. Microvascular complications and foot care. *Diabetes Care* 2016; 39 (Suppl. 1): S72-S80

Recommendations: Diabetic Retinopathy (7)

Treatment (2):

- Intravitreal injections of VEGF are indicated for center-involved diabetic macular edema, which occurs beneath the foveal center and which may threaten reading vision. A
- Retinopathy is not a contraindication to aspirin therapy for cardioprotection, as it does not increase the risk of retinal hemorrhage. A

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American Diabetes Association Standards of Medical Care in Diabetes. Microvascular complications and foot care. *Diabetes Care* 2016; 39 (Suppl. 1): S72-S80

Thank you

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Diabetes Management 2016: Pharmacology

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Presenter Disclosure Information

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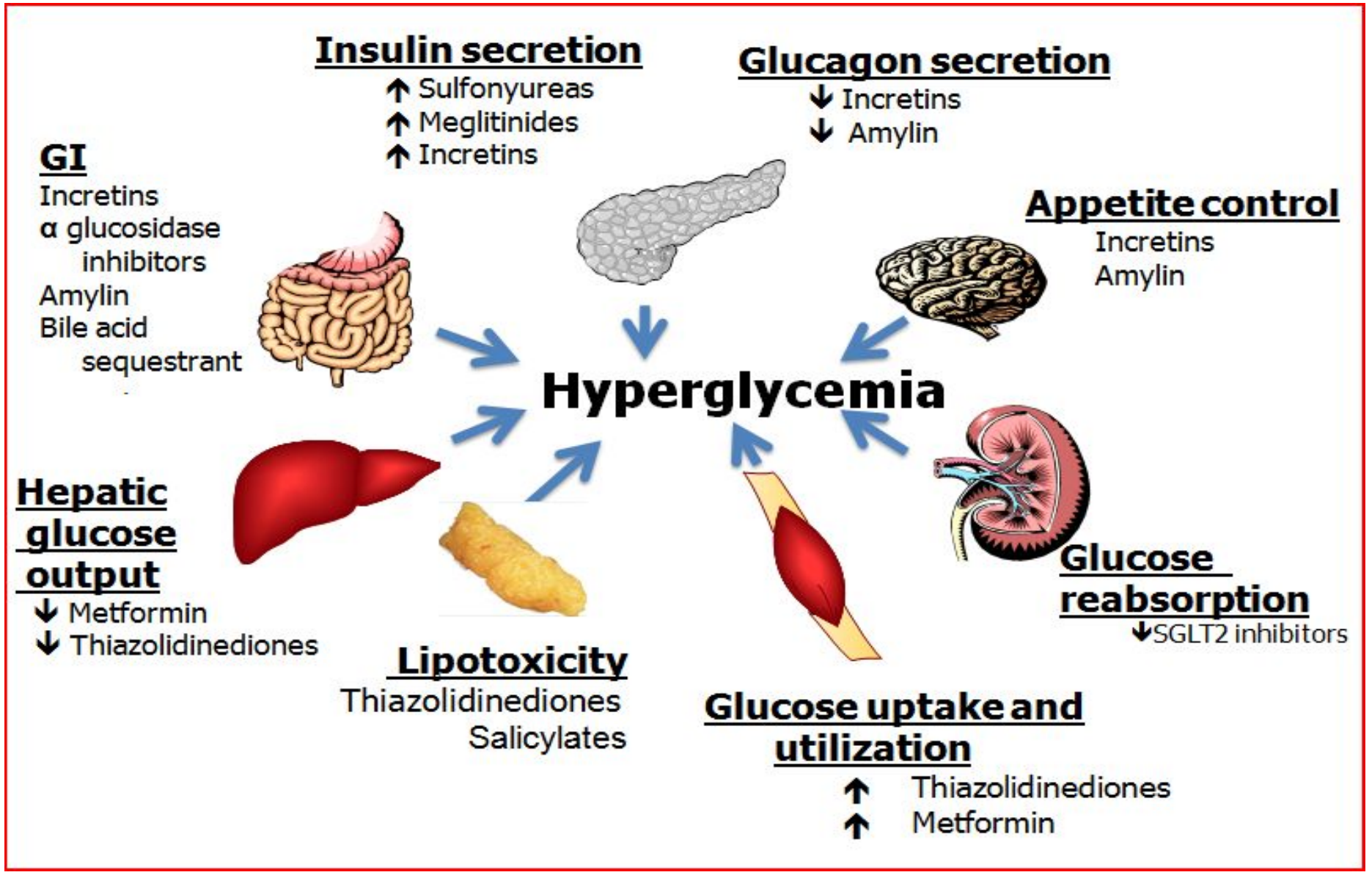
Elizabeth Stephens, MD

Disclosed no conflict of interest

Topics to Discuss:

- Review of pharmacology of medication classes, with updated information
  - Metformin
  - Sulfonylureas
  - Thiazolidinedione
  - Incretins
    - DPP-4
    - GLP-1
  - SGLT-2 inhibitors
  - Insulin

Drugs for DM Management



TYPE 2 DIABETES
12 Different Classes of Therapy

Reduce Hepatic Glucose Production

– Metformin + XR

Enhance Insulin Secretion/Effect

– Sulfonylureas
- glipizide, glyburide, glimepiride

– Meglitinides **(**short acting)
- Repaglinide (Prandin), nateglinide (Starlix**)**

– Insulin- injectable

Attenuate Glucose Absorption

– α-glucosidase inhibitors
- Acarbose (Precose)
- Miglitol (Glyset**)**

Other:

- Bromocriptine
- Salsalate
- Colesevelam
- Amylin Analogs (Symlin)

Insulin Sensitizers

– Thiazolidinediones
- Pioglitazone (Actos) ,Rosiglitazone (Avandia)

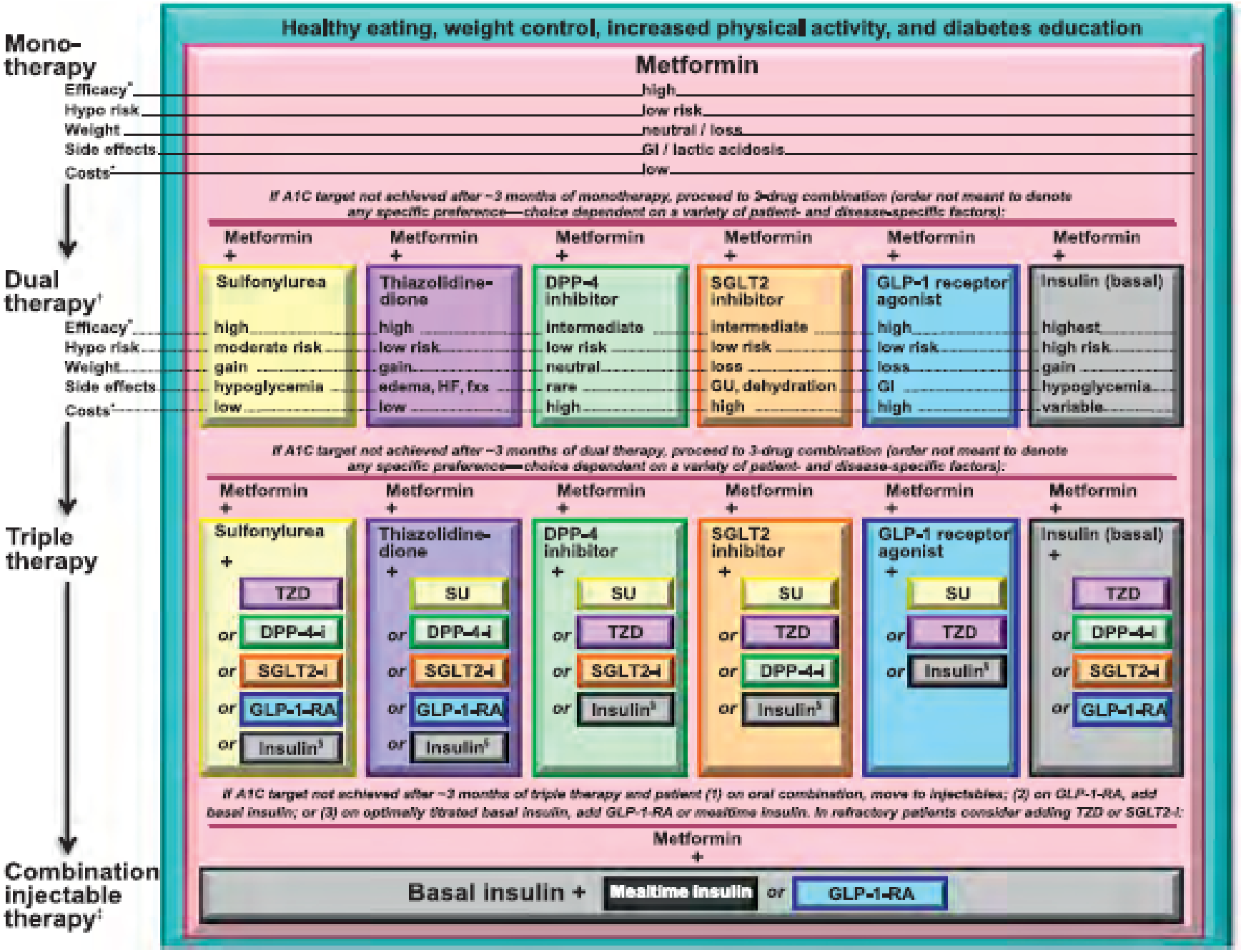
SGLT 2 Inhibitors

- Canagliflozin (Invokana), Dapagliflozin (Farxiga), Empagliflozin (Jardiance)

Incretin Therapies

– *GLP Analogs*
- Exenatide (Byetta), XR weekly
- Liraglutide (Victoza), Albiglutide (Tanzeum), dulaglutide (Trulicity), liraglutide (Saxenda)

– *DPPIV Inhibitors*
- Sitagliptin (Januvia), Saxagliptin (Onglyza), Linagliptin (Tradjenta), Alogliptin (Nesina)



Diab Care 2016;39(supp 1):S52

Metformin

- Mechanism of action (MOA): ↓ hepatic glucose production
- A1c lowering: 1-1.5%
- Cost: $4/month
- Pros:long experience, lack of hypoglycemia, ↓ CVD (UKPDS), ? cancer protection
- Cons: Diarrhea/cramping (?less with XR), B12 deficiency, ? lactic acidosis (very rare), cautious use with comorbidities (acidosis, hypoxia, CHF, **? renal insufficiency**)

FDA Revises Metformin Warnings
NEW Labeling- 2016

- **Then:** Don't use in women Cr ≥1.4mg/dL, Men ≥1.5mg/dL
- **Now**: Before starting metformin, check eGFR
  - Contraindicated if <30mL/min/1.73m2
  - Don't start if between 30-45mL/min/1.73m2
- If eGFR falls to < 45mL/min/1.73m2, assess risk/benefits and consider ↓ dose
- Follow annually, or more often if at risk

www.fda.gov/drugs/drugsafety/ucm493244.htm

Sulfonylureas

- MOA: ↑insulin secretion from beta cells
- A1c lowering: 1-2%
- Cost: Low ($4/month)
- Pros: effective, long-experience,↓micro-vascular risk (UKPDS)
- Cons: **hypoglycemia, weight gain**, **durability,** ? blunts myocardial ischemic preconditioning

More on Sulfonylureas

- Beta cell burnout:
  - ADOPT: lost glucose control at 45months with metformin vs 33 months with glyburide
  - No difference in UKPDS
  - Over 6 yrs, 34% with SU needed insulin, c/w 27% with DPP4
- Weight gain: 2-5kg on average
- Hypoglycemia:
  - 6x more hypoglycemia c/w other DM meds

Kahn S, NEJM 2006;355:427; UKPDS 1995;11:1249; Inzucchi S, Diab Obes Metab 2015; Cefalu W, Diab Care 2015

Thiazolidinediones:

- MOA: ↑ insulin sensitivity
- A1c lowering:1-1.5%
- Cost: low ($30/month + coupon)
- Pros: no hypoglycemia, durable, ↑HDL, ↓TG's, ↓CVD events (PROactive), ?**protective in steatohepatitis**
- Cons: Fluid retention/CHF, weight gain, fractures, ↑LDL, ? MI (rosiglitazone), bladder cancer?

Pioglitazone in Steatohepatitis

- 101 pts with pre-DM or dm, biopsy-proven nonalcoholic steatohepatitis (NASH)
  - Randomized to PBO or pioglitazone 45mg/d for 18 months
- 58% achieved ↓ score of liver disease
  - 51% with resolution of NASH
- Led to reduction in A1c, fasting insulin, AST/ALT, triglycerides
- Also noted: gain of 2.5 kg, no further benefit with longer duration of treatment (up to 36 mos)

Cusi K, Annals IM 2016

DPP 4's

- MOA: Inhibitors of metabolism of GLP1/GIP to enhance incretin effect
- A1C lowering: .5-1%
- Cost: high ($370/month + coupon)
- Pros: less hypoglycemia unless used with SU/insulin, oral, option with renal insufficiency (linagliptin)
- Cons: angioedema/urticaria, ?pancreatitis, ? ↑ **CHF**

GLP-1 Medications

- MOA: ↑insulin secretion,↓glucagon, slows gastric emptying, ↑satiety
- A1C lowering: 1-1.5%
- Cost: high ($580-650/month+coupon)
- Pros: no hypoglycemia, weight loss, **CV benefit**
- Cons: injectable, pancreatitis, GI side effects, medullary thyroid cancer in animals, renal issues (exenatide)

GLP-1 Weekly







- Useful to consider in reluctant injectors
- Equivalent benefit to daily dosing
  - Wt loss, A1c lowering, hypoglycemia, SE
  - Review showed better A1c/wt loss with dulaglutide/weekly exenatide, but data biased (Zaccardi F, Ann IM 2015)
- ***Pick the one tolerated and affordable***

SGLT2 Inhibitors:

- MOA: blocks glucose reabsorption by the kidney->glucosuria
- A1c lowering: .5-1%
- Cost: high ($400/month+coupon)
- Pros: no hypoglycemia, ↓weight, ↓BP, durable, **CV benefit**, renal protection
- Cons: GU infections, polyuria, volume depletion/hypotension, ↑LDL/creatinine

CV Outcomes in DM Medications

- Motivated by high prevalence of CV in diabetes + concerns raised by rosiglitazone
- FDA Guidance to Industry, 2008
  - Sponsors should demonstrate that new type 2 DM drugs should not result in unacceptable CV risk
  - Require inclusion of higher risk CV patients, be long enough to detect adverse CV effects, include in protocol and committees to evaluate

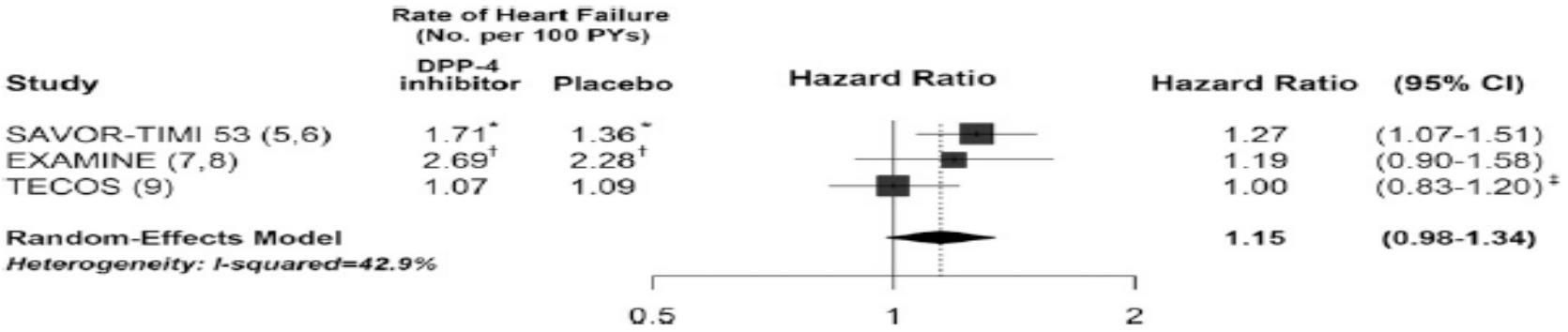
Smith RJ, Diabetes Care 2016

Completed CV Outcome Trials

Trial, n of subjects	MACE*	Hosp for CHF	All-cause mortality
SAVOR-TIMI (saxagliptin), n=16,492	1.00 (.89-1.12)	**1.27 (1.07-1.51)**	1.11 (.96-1.27)
EXAMINE (alogliptin), n=5,380	.96 (.8-1.16)	1.19 (.9-1.58)	.88 (.71-1.09)
TECOS (sitagliptin), N=14,671	.98 (.88-1.09)	1.0 (.83-1.2)	1.01 (.9-1.14)
EMPA-REG (empagliflozin), n=7020	.86 (.74-.99)	**.65 (.5-.8)**	**.68 (.57-.82)**
ELIXA (lixisenatide), n=6,068	1.02 (.89-1.17)	.96 (.82-1.16)	.94 (.78-1.13)
LEADER (liraglutide) n=9340	.87 (.78-.97)	.87 (.73-1.05)	**.85 (.74-.97)**
Sustain 6 (semaglutide) n=3,297	.74 (.58-.95)	1.11 (.77-1.61)	1.05 (.74-1.5)

DPP4's and CHF?

- No increase noted in retrospective cohort of 376,677 pts comparing risks for CHF with saxagliptin/sitagliptin (Toh et al, Annals IM 2016)
- Explanations:
  - Chance finding, differences in studies/patients enrolled, background care provided, differences in drugs



Filion KB, Diab Care 2016

EMPA-REG OUTCOME Trial

- 7028 patients, type 2 DM + CVD
  - Followed 3.1 years
  - Empagliflozin 10mg vs 25mg vs PBO
- Primary outcome:Composite CVD death, non-fatal MI, non-fatal stroke
  - 97% completed study
- With empagliflozin:
  - ↓ rates of CV death from CV causes, CHF admits, death from any cause
  - A1c ↓ : 12 wks: -.54-.6%, 206 wks: -.24-.36%

Zinman B et al, NEJM 2015;373:2117

Results from EMPA-REG

Empagliflozin, 10 mg or 25 mg daily, vs placebo in patients with type 2 diabetes and CVD‡

Outcomes	*Event rates*		*At a median 3.1 y of follow-up*	
	Empagliflozin	*Placebo*	*RRR (95% CI)*	*NNT (CI)*
Primary composite§	10%	12%	13% (1 to 25)	63 (34 to 882)
CV death	3.7%	5.9%	37% (22 to 50)	46 (34 to 76)
Nonfatal MI (excluding silent MI)	4.5%	5.2%	13% (−9 to 29)	Not significant
Secondary composite‖	13%	14%	10% (−1 to 21)	Not significant¶
All-cause mortality	5.7%	8.3%	31% (17 to 42)	39 (29 to 70)
Adverse events**	90%	92%	1.6% (−0.01 to 3)	Not significant††
Serious adverse events**	38%	42%	10% (4 to 15)	24 (16 to 58)
			RRI (CI)	*NNH*
Nonfatal stroke	3.2%	2.6%	24% (−8 to 66)	Not significant

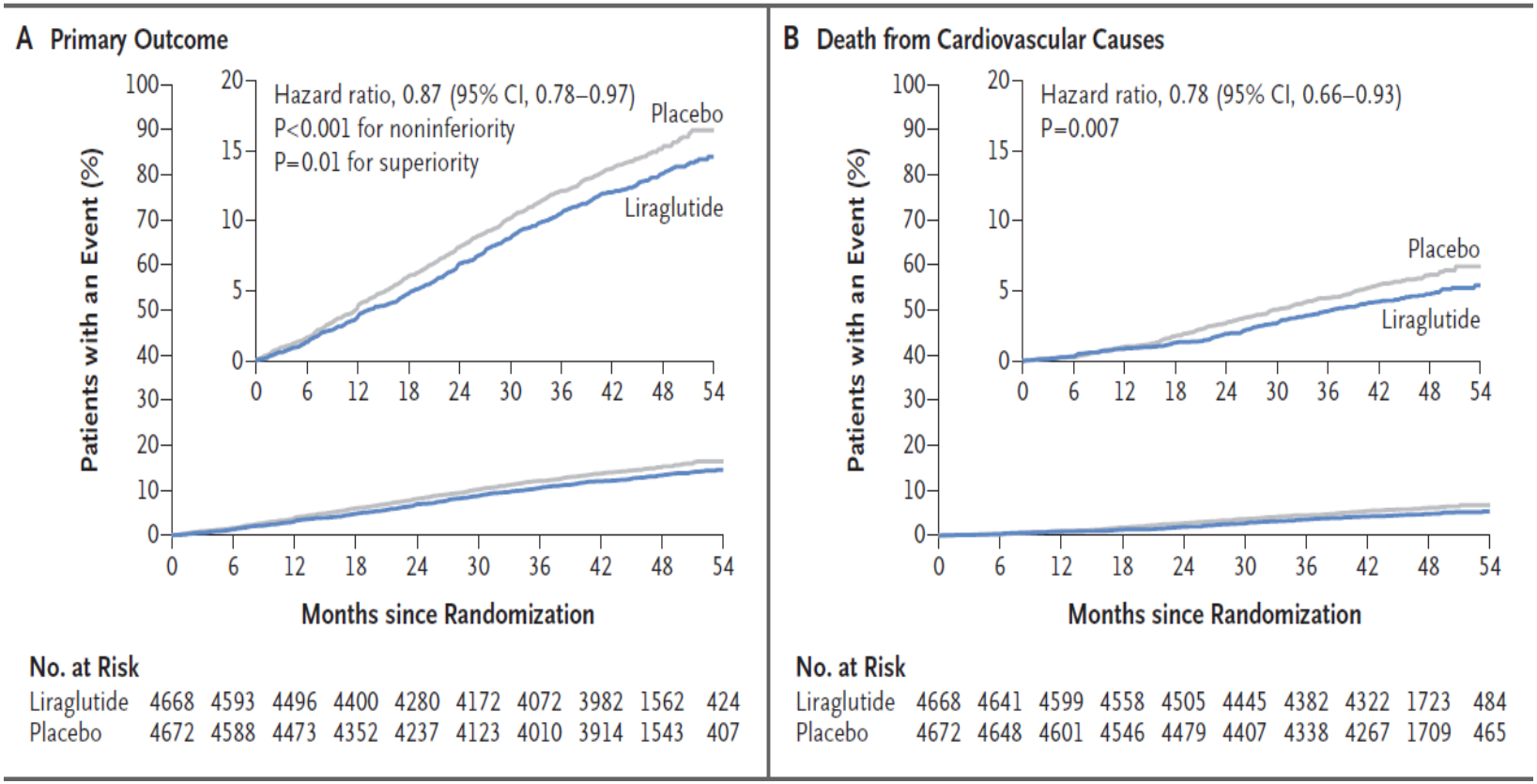
ACP JC 1-19-16

SGLT-2's Cardioprotective?

Effect	Likelihood	Reason
Metabolic actions		
-↓ BG	**Unlikely**	**BG a weak CV risk factor, benefit of A1c on CVD takes 10 yrs**
-↑ fat oxidation or ketone concentration	**Unlikely**	**↑O2 demand per ATP generated**
- Weight loss	**Unlikely**	**Modest changes**
Hemodynamic actions		
-↓ BP	**Likely**	**Proven CV protection in prior studies**
- Diuretic effect	**Likely**	**Proven against CHF in prior trials**
- Impaired arterial elasticity	**Possible**	**? Some effect of empagliflozin**
- Direct effect on myocardium	**Unlikely**	**No evidence**
-Decreased sympathetic tone	**Possible**	**No ↑ in HR with ↓ in BP and volume**

Abdul-Ghani M, Diab Care 2016

Liraglutide and CV Outcomes



LEADER Trial: 9340 pts, followed for 3.8 yrs, randomized to liraglutide or placebo
NNT to prevent one event in 3 yrs was 66 (primary outcome), 98 (death)

Marso SP et al, NEJM 2016

In-Progress CVD Trials

Trial	Med	Planned #	Planned date
SUSTAIN-6	Semaglutide	3297	Jan 2016
CANVAS	Canagliflozin	4407	June 2017
CARMELINA	Linagliptin	8300	Jan 2018
EXSCEL	Exenatide	14000	Jan 2018
ITCA 650	Exenatide	4000	July 2018
CAROLINA	Linagliptin	6000	Sept 2018
DECLARE-TIMI 58	Dapagliflozin	17150	April 2019
REWIND	Dulaglutide	9622	April 2019
HARMONY	Albiglutide	9400	May 2019
CV OUTCOMES ERTUGLIFLOZIN	Ertugliflozin	3900	Oct 2020
CV OUTCOMES OMARIGLIPTIN	Omarigliptin	4202	Dec 2020

Smith RJ, Diab Care 2016

Summary of CVD Data

- Studies note benefit/harm with particular medications
  - Unclear if class effect
- Many payors are responding to this data to make certain brands “preferred”
- Plenty of ongoing trials, so more to come!

New insulin Options

- Degludec (*Tresiba®)*:
  - Comes as U100 or U200
  - Transition 1:1 (consider 20% decrease with BID or lower A1c)
  - Dosing flexibility (not given < every 8 hours)
- U300 Glargine(*Toujeo®)*:
  - Transition 1:1 from long-acting
    - Often requires dose ↑ 10-15% c/w regular glargine
  - Once daily, same time

Clinical Profiles

	Duration of Action	Half-life	Steady State	Max Dose	Units/pen	Pens/box	Cost
U300 Lantus	> 30 hours	18-19 hrs	5 days	80 U	450	3 (1350)	$350
U100 Degludec	42 hrs	25 hrs	2-3 days	80 U (1U adj)	300	5 (1500)	$450
U200 Degludec	42 hrs	25 hrs	2-3 days	160 U (2U adj)	600	3 (1800)	$560

When to consider new insulins? *My opinion…*

- *Degludec*: shift workers, higher dosing requirements, forgetting insulin doses, long-acting twice/day, variability thought due to long-acting
- *U300 glargine*: long-acting twice/day, forgetting insulin doses, variability thought due to long-acting

Combinations instead of bolus?

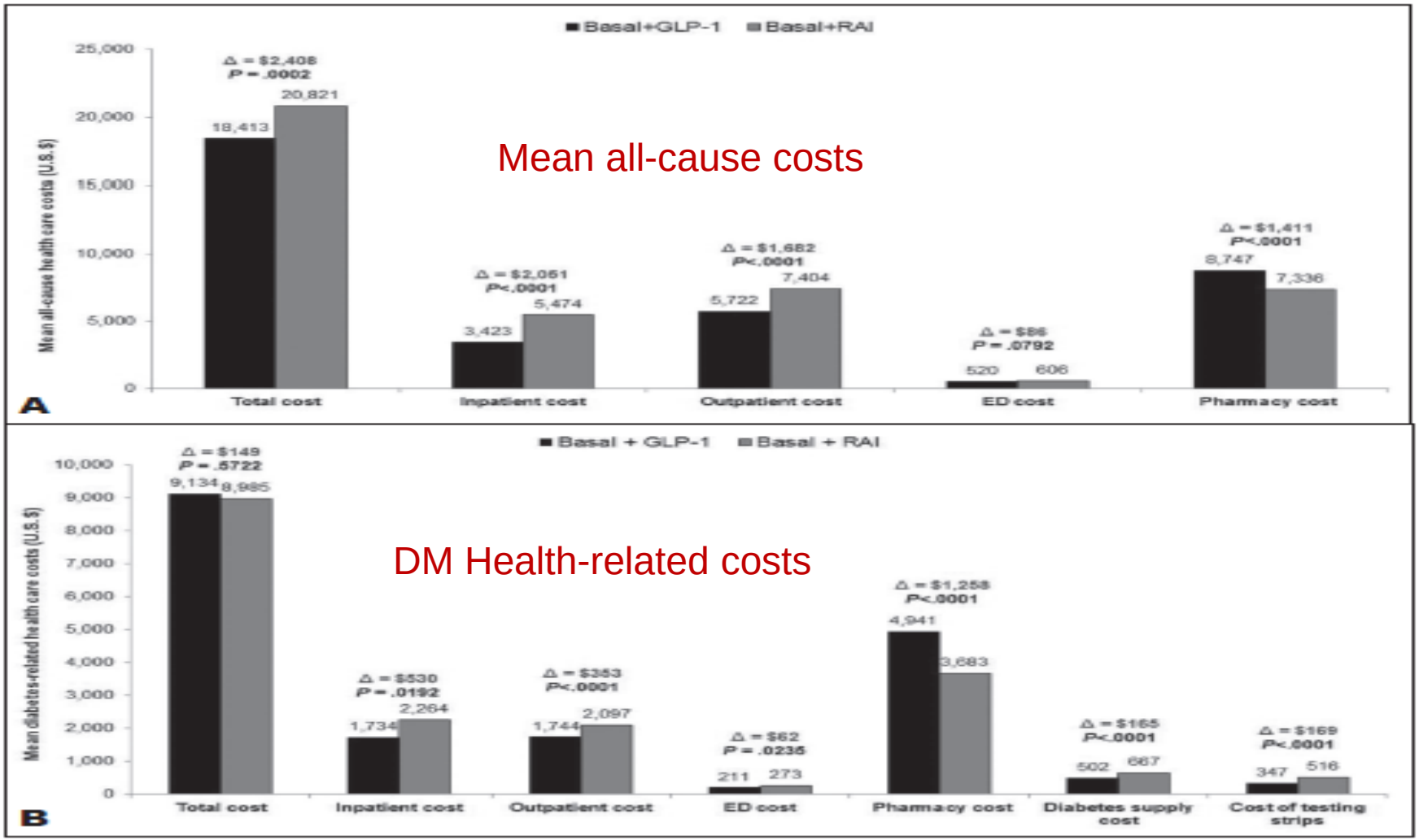
- GLP-1 or SGLT2 inhibitors
  - Effective to control BG + weight loss + ↓ hypoglycemia
- TZD also an option
  - ↑ fluid retention, weight gain when used with insulin

GLP-1 agonists plus basal insulin (GLP-1 combination) vs other antidiabetic treatments (control) in patients with type 2 diabetes*

Outcomes	Number of trials (n)	GLP-1 combination	Control	At 12 to 36 wk†
				Weighted mean difference (95% CI)‡
HbA_{1c} level, %	15 (4348)			−0.44 (−0.60 to −0.29)
Weight change, kg	12 (3941)			−3.2 (−4.9 to −1.5)
		Weighted event rates		RBI (CI)	NNT (CI)
HbA_{1c} level ≤ 7.0%	14 [4267]§	59%	31%	92% (43 to 156)	4 (3 to 8)
				RRR (CI)	NNT
Hypoglycemia	11 (3356)	27.6%	27.9%	1% (−29 to 24)	Not significant

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Cost Data



Mean all-cause costs

DM Health-related costs

Total health costs for $18,413 (GLP1) vs $20,821 (RAI), but diabetes costs were similar.

Dalal MR, Endo Prac 2015

Don’t Overlook NPH and Regular Insulin

- Among privately insured adults + DM2
  - 19% using analogs in 2000, c/w 96% in 2010
  - From 2001 → 2015, lispro vials increased from $35 → $234, human insulin $20 → $131
- LOTS of marketing with insulin analogs
  - Emphasizing more physiologic, less hypoglycemia
- **No difference in A1c, no data on outcomes or complications**

Tylee T, Hirsch I, JAMA 2015

Conclusions

- DM is complicated, on **so** many levels
- Many new medications to choose from
  - Newer isn't necessarily better
    - But lots of direct-to-consumer marketing, so good to have some familiarity
- Cost an ongoing challenge
- More people have diabetes but:
  - Management is improving
  - Fewer complications

PROVIDENCE
Health & Services

THE END

