Standards of Medical Care in Diabetes — 2016

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Portland Diabetes and Endocrine Center
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
2. Classification and 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)
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.
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.
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

Recommendations: Screening for Type 2 Diabetes

- Consider testing in asymptomatic adults of any age with BMI ≥25 kg/m² or ≥23 kg/m² 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
**Recommendations: Detection and Diagnosis of GDM**

- Test for undiagnosed T2DM at the 1\textsuperscript{st} prenatal visit in those with risk factors. \textit{B}

- Test for GDM at 24–28 weeks of gestation in women not previously known to have diabetes. \textit{A}

- Screen women with GDM for persistent diabetes at 6–12 weeks postpartum, using the OGTT. \textit{E}
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**
4. Prevention or Delay of Type 2 Diabetes
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
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/m², aged <60 years, and women with prior gestational diabetes (GDM). A
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
5. Glycemic Targets
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.
Patients on multiple-dose insulin (MDI) or insulin pump therapy should do SMBG:
- 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

Recommendations: Glucose Monitoring

Glucose Monitoring (2)

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
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
## Mean Glucose Levels for Specified A1C Levels

<table>
<thead>
<tr>
<th>A1C%</th>
<th>Mean Plasma Glucose*</th>
<th>Fasting</th>
<th>Premeal</th>
<th>Postmeal</th>
<th>Bedtime</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/dL</td>
<td>mmol/L</td>
<td>mg/dL</td>
<td>mg/dL</td>
<td>mg/dL</td>
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<tr>
<td>6</td>
<td>126</td>
<td>7.0</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;6.5</td>
<td></td>
<td></td>
<td>122</td>
<td>118</td>
<td>144</td>
</tr>
<tr>
<td>6.5-6.99</td>
<td>142</td>
<td>139</td>
<td>164</td>
<td>153</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>154</td>
<td>8.6</td>
<td></td>
<td></td>
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<tr>
<td>7.0-7.49</td>
<td>152</td>
<td>152</td>
<td>176</td>
<td>177</td>
<td></td>
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<tr>
<td>7.5-7.99</td>
<td>167</td>
<td>155</td>
<td>189</td>
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</tr>
<tr>
<td>8</td>
<td>183</td>
<td>10.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-8.5</td>
<td></td>
<td></td>
<td>178</td>
<td>179</td>
<td>206</td>
</tr>
<tr>
<td>9</td>
<td>212</td>
<td>11.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>240</td>
<td>13.4</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>269</td>
<td>14.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>298</td>
<td>16.5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


[professional.diabetes.org/eAG]
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**
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

Approach to the Management of Hyperglycemia

Patient/Disease Features

- Risks associated with hypoglycemia & other drug adverse effects
- Disease Duration
- Life expectancy
- Important comorbidities
- Established vascular complications
- Patient attitude & expected treatment efforts
- Resources & support system

A1C 7%

more stringent → less stringent

<table>
<thead>
<tr>
<th>Patient/Disease Features</th>
<th>low</th>
<th>high</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk associated with hypoglycemia &amp; other drug adverse</td>
<td>newly</td>
<td>long-standing</td>
</tr>
<tr>
<td>effects</td>
<td>diagnosed</td>
<td></td>
</tr>
<tr>
<td>Disease Duration</td>
<td>short</td>
<td></td>
</tr>
<tr>
<td>Life expectancy</td>
<td>short</td>
<td></td>
</tr>
<tr>
<td>Important comorbidities</td>
<td>Few/mild</td>
<td>severe</td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>Few/mild</td>
<td>severe</td>
</tr>
<tr>
<td>Patient attitude &amp; expected treatment efforts</td>
<td>highly motivated, adherent, excellent self-care capabilities</td>
<td>less motivated, nonadherent, poor self-care capabilities</td>
</tr>
<tr>
<td>Resources &amp; support system</td>
<td>readily available</td>
<td>limited</td>
</tr>
</tbody>
</table>

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
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
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
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.
7. Approaches to Glycemic Treatment
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).

Individuals who have been successfully using CSII should have continued access after they turn 65 years old.
8. Cardiovascular Disease and Risk Management
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
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
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
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

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**

<table>
<thead>
<tr>
<th>Age</th>
<th>Risk Factors</th>
<th>Statin Intensity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>ASCVD risk factor(s)**</td>
<td>Moderate or high</td>
</tr>
<tr>
<td></td>
<td>ASCVD</td>
<td>High</td>
</tr>
<tr>
<td>40–75 years</td>
<td>None</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>ASCVD risk factors</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>ACS &amp; LDL &gt;50 who can’t tolerate high dose statin</td>
<td>Moderate + ezetimibe</td>
</tr>
<tr>
<td>&gt;75 years</td>
<td>None</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>ASCVD risk factors</td>
<td>Moderate or high</td>
</tr>
<tr>
<td></td>
<td>ASCVD</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>ACS &amp; LDL &gt;50 who can’t tolerate high dose statin</td>
<td>Moderate + ezetimibe</td>
</tr>
</tbody>
</table>

* 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.
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
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**
# High- and Moderate-Intensity Statin Therapy*

<table>
<thead>
<tr>
<th>High Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowers LDL by ≥50%</td>
<td>Lowers LDL by 30 - &lt;50%</td>
</tr>
<tr>
<td>Atorvastatin 40-80 mg</td>
<td>Atorvastatin 10-20 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20-40 mg</td>
<td>Rosuvastatin 5-10 mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20-40 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40-80 mg</td>
</tr>
<tr>
<td></td>
<td>Lovastatin 40 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin XL 80 mg</td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 2-4 mg</td>
</tr>
</tbody>
</table>

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

- 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
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
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
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.
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
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
Thank you
Diabetes Management 2016: Pharmacology

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November 2016
Presenter Disclosure Information

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

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

**Insulin secretion**
- **↑** Sulfonyureas
- **↑** Meglitinides
- **↑** Incretins

**Glucagon secretion**
- **↓** Incretins
- **↓** Amylin

**GI**
- Incretins
- α glucosidase inhibitors
- Amylin
- Bile acid sequestrant

**Appetite control**
- Incretins
- Amylin

**Hepatic glucose output**
- **↓** Metformin
- **↓** Thiazolidinediones

**Lipotoxicity**
- Thiazolidinediones
- Salicylates

**Glucose uptake and utilization**
- **↓** Thiazolidinediones
- **↑** Metformin

**Glucose reabsorption**
- **↓** SGLT2 inhibitors

**Hyperglycemia**
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)
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, ↓microvascular risk (UKPDS)
- Cons: hypoglycemia, weight gain, durability, ? blunts myocardial ischemic preconditioning
More on Sulfonylureas

• Beta cell burnout:
  – ADOPT: lost glucose control at 45 months 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

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

---

<table>
<thead>
<tr>
<th>Study</th>
<th>Rate of Heart Failure (No. per 100 PYs)</th>
<th>Hazard Ratio</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DPP-4 inhibitor</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>SAVOR-TIMI 53 (5,6)</td>
<td>1.71*</td>
<td>1.36*</td>
<td>1.27</td>
</tr>
<tr>
<td>EXAMINE (7,8)</td>
<td>2.69†</td>
<td>2.28†</td>
<td>1.19</td>
</tr>
<tr>
<td>TECOS (9)</td>
<td>1.07</td>
<td>1.09</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Random-Effects Model

Heterogeneity: I-squared=42.9%

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‡**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Event rates</th>
<th>At a median 3.1 y of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Empagliflozin</td>
<td>Placebo</td>
</tr>
<tr>
<td>Primary composite§</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>CV death</td>
<td>3.7%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Nonfatal MI (excluding silent MI)</td>
<td>4.5%</td>
<td>5.2%</td>
</tr>
<tr>
<td>Secondary composite</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>5.7%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Adverse events**</td>
<td>90%</td>
<td>92%</td>
</tr>
<tr>
<td>Serious adverse events**</td>
<td>38%</td>
<td>42%</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>3.2%</td>
<td>2.6%</td>
</tr>
</tbody>
</table>
# SGLT-2’s Cardioprotective?

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

Abdul-Ghani M, Diab Care 2016
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

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

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

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

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Number of trials (n)</th>
<th>GLP-1 combination</th>
<th>Control</th>
<th>At 12 to 36 wk†</th>
<th>Weighted mean difference (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c level, %</td>
<td>15 (4348)</td>
<td></td>
<td>-0.44 (-0.60 to -0.29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight change, kg</td>
<td>12 (3941)</td>
<td></td>
<td>-3.2 (-4.9 to -1.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weighted event rates</th>
<th>RBI (CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c level ≤ 7.0%</td>
<td>59%</td>
<td>31%</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>27.6%</td>
<td>27.9%</td>
</tr>
</tbody>
</table>
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
THE END