Objectives

- Detail factors contributing to cardiovascular disease: hyperlipidemia, hypertension and hyperglycemia
- Review current clinical practice guidelines for the cardiovascular risk factors in diabetes
- Examine cardiovascular outcome trial data for diabetes medications
- Identify newly approved diabetes medications
Cardiovascular risk and diabetes

Contributing factors

Hyperlipidemia
Hypertension
Hyperglycemia

Cardiovascular disease
Blood pressure control in T2DM

- Systolic blood pressure goal:
  - Average patient <140mmHg
  - High risk CVD <130mmHg
- Diastolic blood pressure goal:
  - Average patient <90mmHg
  - High risk CVD <80mmHg
- Hypertensive patients without albuminuria are equally recommended any of the following: ACE-I, ARBs, DHP-CCB, and thiazide-like diuretics.

Lipid management

- Glycemic control is intensified in individuals with:
  - Triglyceride levels >150 mg/dL
  - HDL <40 mg/dL in men; <50 mg/dL in women
- Screening lipid profile is recommended for diabetics not taking statins:
  - At diabetes diagnosis
  - Every 5 years thereafter
- Initiation of moderate or high intensity statin therapy
- No niacin; limited benefit to fibrates
Statin therapy in T2DM

<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, ASCVD risk factor(s), ASCVD</td>
<td>None, Moderate or high High</td>
</tr>
<tr>
<td>40–75 years</td>
<td>None, ASCVD risk factors, ACS &amp; LDL ≥50 or in patients with history of ASCVD who can’t tolerate high dose statin</td>
<td>Moderate, High, Moderate + ezetimibe</td>
</tr>
<tr>
<td>&gt;75 years</td>
<td>None, ASCVD risk factors, ASCVD, ACS &amp; LDL ≥50 or in patients with history of ASCVD who can’t tolerate high dose statin</td>
<td>Moderate, Moderate or high, High, Moderate + ezetimibe</td>
</tr>
</tbody>
</table>

American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

Patients >21 yr of age without heart failure (NYHA class II, III, or IV) or end-state renal disease (undergoing hemodialysis) Screen for cardiovascular risk factors. Measure LDL cholesterol

Clinical atherosclerotic CVD

Diabetes mellitus and age of 45-75 yr and LDL cholesterol 70-189 mg/dl

No diabetes mellitus and age of 45-75 yr and LDL cholesterol 70-189

LDL cholesterol ≥ 190 mg/dl

High-intensity statin therapy

Calculate 10-yr risk of atherosclerotic CVD

Calculate 10-yr risk of atherosclerotic CVD

High-intensity statin therapy

Unless >75 yo, then moderate-intensity

If risk < 7.5%, moderate-intensity statin therapy. If risk ≥ 7.5%, high-intensity statin therapy

If risk ≥ 7.5%, moderate-to-high intensity statin therapy

Unless >75 yo, then moderate-intensity

### Statin intensity

#### High-intensity:
- Atorvastatin 40-80 mg
- Rosuvastatin 20-40 mg

#### Moderate-intensity:
- Atorvastatin 10-20 mg
- Rosuvastatin 5-10 mg
- Simvastatin 20-40 mg
- Pravastatin 40-80 mg
- Lovastatin 40-80 mg
- Fluvastatin 80 mg
- Pitavastatin 2-4 mg


### Antiplatelet therapy

- **Secondary ASCVD prevention**:
  - Aspirin therapy: 75-162 mg/day
  - Clopidogrel: 75 mg/day (if aspirin allergy)
    - Dual antiplatelet therapy can be used for a year following an acute coronary syndrome.

- **Primary ASCVD prevention**
  - Age ≥ 50 years plus risk factor
    - Family history of premature CV disease, hypertension, dyslipidemia, smoking, albuminuria

American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87
Anti-hyperglycemic therapy in T2DM

At diagnosis:
- Lifestyle + Metformin
- Metformin + Basal insulin
- Lifestyle + Metformin + Sulfonylurea
- Lifestyle + Metformin + Intensive insulin
- Lifestyle + Metformin + Pioglitazone
- Lifestyle + Metformin + GLP-1 agonist

Tier 1: Well validated core therapies
- Lifestyle + Metformin + Basal insulin

Tier 2: Less well validated therapies
- Lifestyle + Metformin + Pioglitazone
- Lifestyle + Metformin + Sulfonylurea
- Lifestyle + Metformin + Basal insulin

2009 ADA / EASD algorithm

### 2017 ADA algorithm

#### Monotherapy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Efficacy</th>
<th>Hypoglycemia</th>
<th>Weight</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>High</td>
<td>Low risk</td>
<td>Neutral loss</td>
<td>G/lactic acidosis</td>
</tr>
</tbody>
</table>

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient & disease-specific factors).

#### Dual Therapy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Efficacy</th>
<th>Hypoglycemia</th>
<th>Weight</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT2 Inhibitor + DPP-4 inhibitor</td>
<td>Intermediate</td>
<td>Low risk</td>
<td>Neutral</td>
<td>High</td>
</tr>
</tbody>
</table>

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient & disease-specific factors).

### Triple Therapy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Efficacy</th>
<th>Hypoglycemia</th>
<th>Weight</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 RA + SGLT2 Inhibitor + DPP-4 inhibitor</td>
<td>Low risk</td>
<td>Intermediate</td>
<td>Neutral</td>
<td>High</td>
</tr>
</tbody>
</table>

### Glycemic Control Algorithm

**Lifestyle Therapy** (including Medically Assisted Weight Loss)

*Order of medication represents a suggested hierarchy of use depending on the effectiveness of management.*

#### MONOTHERAPY

**Metformin**

- If not at goal in 3 months, proceed to Dual Therapy
- First aim in 3 months, proceed to Triple Therapy

#### DUAL THERAPY

- GLP-1 RA
- SGLT2 Inhibitor
- DPP-4 Inhibitor
- TZD
- Basal insulin
- GLP-1 RA + SGLT2 Inhibitor
- GLP-1 RA + DPP-4 Inhibitor
- GLP-1 RA + TZD
- GLP-1 RA + Basal insulin
- GLP-1 RA + SGLT2 Inhibitor + DPP-4 Inhibitor
- GLP-1 RA + SGLT2 Inhibitor + TZD
- GLP-1 RA + SGLT2 Inhibitor + Basal insulin

#### TRIPLE THERAPY

- GLP-1 RA + SGLT2 Inhibitor + TZD
- GLP-1 RA + SGLT2 Inhibitor + Basal insulin
- GLP-1 RA + SGLT2 Inhibitor + DPP-4 Inhibitor
- GLP-1 RA + SGLT2 Inhibitor + DPP-4 Inhibitor + TZD
- GLP-1 RA + SGLT2 Inhibitor + DPP-4 Inhibitor + Basal insulin

**Progression of Disease**

*Copyright © 2016 ADA. Was not reproduced in any form without express written permission from ADA.*
Combination injectable therapy in T2DM

**Initiate Basal Insulin**
Usually with metformin +/- other noninsulin agent

- **Start:** 10 U/day or 0.1-0.2 U/kg/day
- **Adjust:** 10-15% or 2-4 units once or twice weekly to reach FBG target
- **For hypo:** Determine + address cause; if no clear reason, ↓
corresponding dose 4U or 10-20%

If A1c not controlled, consider combination injectable therapy

- **Add 1 rapid-acting insulin injection before largest meal**
- **Add GLP-1 RA**
- **Change to premixed insulin twice daily (before breakfast and supper)**

Large non-insulin CVOTs in T2DM

<table>
<thead>
<tr>
<th>Study</th>
<th>LEADER</th>
<th>ELIXA</th>
<th>SUSTAIN 6</th>
<th>EXCEL</th>
<th>REWIND</th>
<th>FREEDOM</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP1-RA</td>
<td>liraglutide</td>
<td>exenatide</td>
<td>semaglutide</td>
<td>exenatide LR</td>
<td>dulaglutide</td>
<td>TFC-550</td>
</tr>
<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
</tr>
<tr>
<td>N</td>
<td>10,000</td>
<td>6,000</td>
<td>5,400</td>
<td>5,400</td>
<td>5,400</td>
<td>5,400</td>
</tr>
</tbody>
</table>

- **NEUTRAL**
- **POSITIVE**
- **NEGATIVE**

CVOT: Cardiovascular Outcomes Trial.
CVD data: GLP-1 agonists

GLP-1 agonists
Properties of GLP-1 agonists

<table>
<thead>
<tr>
<th>Parameter</th>
<th>exenatide twice daily (Byetta)</th>
<th>liraglutide daily (Victoza)</th>
<th>ER exenatide weekly (Bydureon)</th>
<th>albiglutide weekly (Tanzeum)</th>
<th>dulaglutide weekly (Trulicity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Synthetic exendin-4</td>
<td>Human GLP-1 analog</td>
<td>Exenatide extended release</td>
<td>Human GLP-1 analog</td>
<td>Human GLP-1 analog</td>
</tr>
<tr>
<td>Half-life</td>
<td>2-4 h</td>
<td>12-14 h</td>
<td>&gt; 1 wk</td>
<td>~ 5 days</td>
<td>~ 5 days</td>
</tr>
<tr>
<td>Dosing</td>
<td>5mcg SQ BID Increase to 10mcg BID</td>
<td>0.6mg Qday Increase to 1.2-1.8 mg Qday</td>
<td>2mg Qweek</td>
<td>30mg Qweek Increase to 50mg Qweek</td>
<td>0.75mg - 1.5mg Qweek</td>
</tr>
<tr>
<td>↓ % A1C</td>
<td>~0.9-1.1%</td>
<td>~1.1-1.6%</td>
<td>~1.1-1.3%</td>
<td>~1-1.3%</td>
<td>0.9-1.1%</td>
</tr>
<tr>
<td>↓ Weight</td>
<td>0-5kg decrease across studies dependent on study duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most common AE</td>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GLP-1 agonists – CV effects

- ↓ BP (esp. SBP) independent of weight loss
- ↓ TGs ≥ 20%
- ↓ C-reactive protein, plasminogen activator inhibitor, brain natriuretic peptide
- Promote vasodilation
- Improve endothelial function
- ↑ sodium excretion
- Modestly ↑ heart rate
- Weight loss - ~85% 1-3 kg over 6 months
The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcomes Results (LEADER):

Assessed use of GLP-1 agonist: Liraglutide in the reduction of CVD events among T2DM:

- Primary outcome: MI, stroke, or CV death occurred in fewer patients when treated with liraglutide.

Clinical trials: LEADER

LEADER-Primary outcome

CV death, non-fatal myocardial infarction, or non-fatal stroke

*HR: 0.87*  
95% CI (0.78 – 0.97)  
p=0.001 for non-inferiority  
p=0.01 for superiority
LEADER: Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of patients (%)</th>
<th>Hazard ratio (CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>608 (13.0)</td>
<td>694 (14.9)</td>
<td>0.97 (0.78-0.97)</td>
</tr>
<tr>
<td>Expended composite outcome</td>
<td>948 (20.3)</td>
<td>1062 (22.7)</td>
<td>0.88 (0.81-0.96)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>381 (8.2)</td>
<td>447 (9.6)</td>
<td>0.85 (0.74-0.97)</td>
</tr>
<tr>
<td>Death from CV causes</td>
<td>219 (4.7)</td>
<td>278 (6.0)</td>
<td>0.79 (0.68-0.93)</td>
</tr>
</tbody>
</table>

CVD data: SGLT-2 Inhibitors

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.
SGLT-2 inhibitors

- **MOA:**
  - SGLT-2 Inhibitors work to competitively inhibit glucose reabsorption in the proximal convoluted tubules
  - Glucose subsequently spilled into the urine and is unavailable for metabolism
  - There is an 80% ↓ in reabsorption

- **Efficacy**
  - A1C lowered 0.77-1.16%

SGLT-2 Products
- canagliflozin (Invokana)
  - eGFR > 60
  - 100-300 mg PO daily
  - eGFR 45-59; 100 mg max
- dapagliflozin (Farxiga)
  - eGFR > 60 ml/min
  - 5-10 mg PO daily
- empagliflozin (Jardiance)
  - eGFR > 45 ml/ min
  - 10-25 mg PO daily

SGLT-2 Combination products
- canagliflozin / metformin (Invokanamet)
- dapagliflozin / metformin (Xigduo XR)
- empagliflozin / metformin (Synjardy)
- empagliflozin / linagliptin (Glyxambi)
### Benefits of SGLT-2 inhibitors

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Cangliiflozin</th>
<th>Empagliflozin</th>
<th>Dapagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure reduction</td>
<td>100mg dose vs. placebo: by 3.7mmHg</td>
<td>25mg dose: by 4.2 mmHg</td>
<td>10mg dose vs placebo: adjusted mean change from baseline -11.90 mmHg vs. -7.62 mmHg</td>
</tr>
<tr>
<td>300mg dose vs. placebo: by 5.4mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td>100mg/ 300mg doses: &gt;5-10% weight reduction</td>
<td>25mg dose: ~4.2kg weight reduction</td>
<td>10mg dose: 5% weight reduction</td>
</tr>
</tbody>
</table>

### SGLT-2 inhibitors

#### Advantages
- Weight loss
- BP reduction
- Rare hypoglycemia
- Once daily oral dosing

#### Disadvantages
- Expensive
- Polyuria
- Orthostatic symptoms
- Genital yeast infection
- UTI
Clinical trials: EMPA-REG OUTCOME

- The BI 10773 Empagliflozin Cardiovascular Outcome Event Trial in T2DM (EMPA-REG OUTCOME)
  - Patients with established cardiovascular disease
  - Randomized to empagliflozin or placebo plus standard of care.
  - 3.1 year median follow up


Clinical outcomes with empagliflozin

Clinical Outcomes with Empagliflozin

<table>
<thead>
<tr>
<th>Event</th>
<th>EMPA-REG OUTCOME Pooled Analysis (N=7020)</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint*</td>
<td>14%</td>
<td>0.86 (0.74-0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Secondary composite endpoint†</td>
<td>32%</td>
<td>0.89 (0.78-1.01)</td>
<td>0.08</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>36%</td>
<td>0.68 (0.57-0.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV death</td>
<td>35%</td>
<td>0.62 (0.49-0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fatal or nonfatal MI</td>
<td>35%</td>
<td>0.87 (0.70-1.09)</td>
<td>0.23</td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>34%</td>
<td>0.65 (0.50-0.85)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hospitalization for HF or CV death</td>
<td>34%</td>
<td>0.66 (0.55-0.79)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

EMPA-REG: CV death

Cumulative incidence function. HR, hazard ratio


EMPA-REG: Therapeutic considerations

- Reduction in outcome of MI and stroke by 14% and cardiovascular death by 38%
- Empagliflozin, used in this trial for 3 years in 1,000 patients with T2DM who were at high risk for CVD:
  - 25 lives saved (82 vs. 57 deaths)
  - 22 fewer CV deaths (59 vs. 37)
  - 14 fewer hospitalizations for CHF (42 vs. 28)
  - 53 additional genital infections (22 vs. 75)

New antidiabetic medication products

Comparison of new basal insulins

<table>
<thead>
<tr>
<th></th>
<th><strong>Insulin Degludec (Tresiba)</strong></th>
<th><strong>insulin Glargine (Toujeo)</strong></th>
<th><strong>Insulin Glargine (Basaglar)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of Action</td>
<td>~ 1 hour</td>
<td>~ 2-3 hours</td>
<td>~ 1 hours</td>
</tr>
<tr>
<td>Duration of Action</td>
<td>~ 42 hours</td>
<td>24 hours</td>
<td>~ 24 hours</td>
</tr>
<tr>
<td>Available Concentration</td>
<td>100 IU/ML, 200 IU/ML</td>
<td>300 IU/ML</td>
<td>100 IU/ML</td>
</tr>
<tr>
<td>Pen Devices</td>
<td><img src="image1" alt="Insulin Pen 1" /></td>
<td><img src="image2" alt="Insulin Pen 2" /></td>
<td><img src="image3" alt="Insulin Pen 3" /></td>
</tr>
<tr>
<td>Cost</td>
<td>~$520 / 15 ml</td>
<td>~$391 / 15 mL</td>
<td>~$387 / 15 mL</td>
</tr>
</tbody>
</table>
Lixisenatide/glargine 100/33 (Soliqua)

- 100 units glargine + 33 mcg lixisenatide / ml
- Once daily within one hour before first meal
- Initial dosing
  - Uncontrolled on < 30 units basal insulin
    - 15 units / 5mcg
  - Uncontrolled on ≥ 30 units basal insulin
    - 30 units of Soliqua®
- Titrate weekly dose by 2-4 units to goal
- Max dose 60 units (60 units glargine, 20 mcg lixi)

Lixisenatide plus insulin glargine

Changes in HbA1c over 30 weeks

Diabetes Care. 2016; 39: 2030
Lixisenatide plus insulin glargine

Changes in body weight over 30 weeks

Diabetes Care. 2016; 39: 2030

- 100 units degludec + 3.6 mg liraglutide / ml
- Approved November 2016
- Fixed doses per step; once daily
- Starting dose=16 units (16u degludec and 0.58 mg liraglutide)
- Titrate weekly dose by 2-4 units to goal
- Max dose 50 units (50u degludec, 1.8 mg liraglutide)

Liraglutide/degludec 100/3.6 (Xultophy®)
Liraglutide plus insulin degludec

References