Glucose Lowering Medications and CV Risk Reduction: A New Era

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University of Colorado Anschutz Medical Campus
VA Staff Physician and Merit Investigator

$1 in 4
30.3 Million
24/7/365
CONSIDERATIONS:

• Patient Centered
• Phenotype Centered
• Glucose management is complex and imperfect
• New recommendations for the ~20% DM + CVD
• EASD-ADA updates
Disclosures

• Investigator Initiated Trial Support:
  – Merck: Sitagliptin impact on exercise capacity (T2D)
• Funding: NIH, VA
• Consultant:
  – Oramed
• Board of Directors
  – ADA
Diabetes Shortens Life Span

Age of onset

CVD CHF Tailored Therapy

Premature mortality persists in people with DM

Framingham

Intensive multifactorial treatment (STENO-2)


CVOT History: Why now? Worth it?
In light of premature CV mortality we need to get this right

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
<th>Safety concerns and response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>Human proinsulin</td>
<td>Trials and development suspended &lt;br&gt; <em>CV issues and ↑ risk of acute myocardial infarction</em>&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2005</td>
<td>Muraglitazar</td>
<td><em>↑ Risk of death, major CV adverse events, CHF</em>&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2007</td>
<td>Rosiglitazone</td>
<td><em>↑ CV risk; withdrawn from market in many countries</em>&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2008</td>
<td>–</td>
<td>FDA issued guidance document for the evaluation of CV risk&lt;sup&gt;d&lt;/sup&gt;&lt;br&gt;Studies are required to demonstrate that <em>new anti-diabetic therapies do not increase CV</em> risk in comparison with existing therapies</td>
</tr>
</tbody>
</table>

CVOT are designed and powered to assess *non-inferiority versus placebo* in addition to *standard of care* in a *high risk CVD patient population* (prior CVD ± high risk patients without proven CVD).

**Major endpoint composite of Major Adverse Cardiovascular Events:**
- Usual is 3 point MACE – new nonfatal MI, new stroke, CV death based on careful adjudication to confirm accuracy of the events*

**Key understandings:**
- Powered for safety.
- Studied populations provide data on SECONDARY PROTECTION.
- Original studies not powered for subgroup analysis
- Different design does not consistently enable direct comparison of results of one study to another.
Antihyperglycemic Therapy: Safety and CVD/CHF considerations

- Insulin:
  - ORIGIN trial (Glargine U-100).
  - DEVOTE trial (Degludec vs. Glargine U-100).
- Thiazolidinediones:
  - PROACTIVE trial (Pioglitazone).
  - RECORD trial (Rosiglitazone).
- DPP-4 inhibitor:
  - SAVOR TIMI (Saxagliptin).
  - EXAMINE (Alogliptin).
  - TECOS (Sitagliptin)
## DPP-4 Inhibitor CVD Outcome Trials

<table>
<thead>
<tr>
<th>Agent</th>
<th>Population</th>
<th>Composite Outcome</th>
<th>Key Finding</th>
<th>Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saxagliptin SAVOR TIMI</td>
<td>CVD or risk factors</td>
<td>3 point MACE</td>
<td>Safety HR 1.00</td>
<td>Increased HR 1.27</td>
</tr>
<tr>
<td>Alogliptin EXAMINE</td>
<td>CVD</td>
<td>3 point MACE</td>
<td>Safety HR 0.96</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Sitiglipitin TECOS</td>
<td>CVD</td>
<td>4 point MACE</td>
<td>Safety HR 0.98</td>
<td>Unchanged</td>
</tr>
</tbody>
</table>

Saxagliptin SAVOR TIMI: 3 point MACE, Safety HR 1.00, Increased HR 1.27
Alogliptin EXAMINE: 3 point MACE, Safety HR 0.96, Unchanged
Sitiglipitin TECOS: 4 point MACE, Safety HR 0.98, Unchanged

Beyond Safety

SGLT2 inhibitors

GLP1 Receptor Agonists
## EMPA-REG: CV Death, MI, and Stroke

### Patients With Event/Analyzed

<table>
<thead>
<tr>
<th></th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>HR</th>
<th>(95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point MACE</td>
<td>490/4687</td>
<td>282/2333</td>
<td>0.86</td>
<td>(0.74-0.99)*</td>
<td>.0382</td>
</tr>
<tr>
<td>CV death</td>
<td>172/4687</td>
<td>137/2333</td>
<td>0.62</td>
<td>(0.49-0.77)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>213/4687</td>
<td>121/2333</td>
<td>0.87</td>
<td>(0.70-1.09)</td>
<td>.2189</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>150/4687</td>
<td>60/2333</td>
<td>1.24</td>
<td>(0.92-1.67)</td>
<td>.1638</td>
</tr>
</tbody>
</table>

### Heart Failure

<table>
<thead>
<tr>
<th></th>
<th>Patients With Event, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>7%</td>
</tr>
</tbody>
</table>

*95.02% CI.


[Graph showing the comparison between Empagliflozin and Placebo for CV death, MI, and Stroke events.]

Favors empagliflozin  Favors placebo
EMP A-REG: CV Death

HR: 0.62 (95% CI: 0.49-0.77); $P < .0001$

EMPA-REG: Hospitalization for Heart Failure

HR: 0.65
(95% CI: 0.50-0.85);
\( P = .002 \)

CANAAS and CANVAS-R Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Canagliflozin (N=5795)</th>
<th>Placebo (N=4347)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke</td>
<td>26.9</td>
<td>31.5</td>
<td>0.86 (0.75–0.97)</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>11.6</td>
<td>12.8</td>
<td>0.87 (0.72–1.06)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>9.7</td>
<td>11.6</td>
<td>0.85 (0.69–1.05)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>7.1</td>
<td>8.4</td>
<td>0.90 (0.71–1.15)</td>
</tr>
<tr>
<td>Fatal or nonfatal myocardial infarction</td>
<td>11.2</td>
<td>12.6</td>
<td>0.89 (0.73–1.09)</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>7.9</td>
<td>9.6</td>
<td>0.87 (0.69–1.09)</td>
</tr>
<tr>
<td>Hospitalization for any cause</td>
<td>118.7</td>
<td>131.1</td>
<td>0.94 (0.88–1.00)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>5.5</td>
<td>8.7</td>
<td>0.67 (0.52–0.87)</td>
</tr>
<tr>
<td>Death from cardiovascular causes or hospitalization for heart failure</td>
<td>16.3</td>
<td>20.8</td>
<td>0.78 (0.67–0.91)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>17.3</td>
<td>19.5</td>
<td>0.87 (0.74–1.01)</td>
</tr>
<tr>
<td>Progression of albuminuria</td>
<td>89.4</td>
<td>128.7</td>
<td>0.73 (0.67–0.79)</td>
</tr>
<tr>
<td>40% reduction in eGFR, renal-replacement therapy, or renal death</td>
<td>5.5</td>
<td>9.0</td>
<td>0.60 (0.47–0.77)</td>
</tr>
</tbody>
</table>

CVD-REAL Study

• Real world study of 6 countries (US, Norway, Denmark, Sweden, Germany, UK) for relative rates death and hospitalization for heart failure in pts. newly started on SGLT2i or matched controls (n=154,528 in both).
  – Baseline 3% HF, 13% CVD, 27% microvascular disease.
  – Canagliflozin 53%, Dapagliflozin 42%, Empagliflozin 5%.

• Lowered relative rates in SGLT2i patients:
  – Heart failure – 0.61 (95% CI 0.51-0.73, p<0.001).
  – All cause death – 0.49 (95% CI 0.41-0.57, p<0.001).

• No significant heterogeneity by country.

Who are the people in CVOT studies?
## EMPA-REG: Baseline Characteristics T2D

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 2333)</th>
<th>Empagliflozin 10 mg (n = 2345)</th>
<th>Empagliflozin 25 mg (n = 2342)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c, %</strong></td>
<td>8.08 (0.84)</td>
<td>8.07 (0.86)</td>
<td>8.06 (0.84)</td>
</tr>
<tr>
<td><strong>Time since diagnosis of type 2 diabetes, y</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 5</td>
<td>423 (18.1)</td>
<td>406 (17.3)</td>
<td>434 (18.6)</td>
</tr>
<tr>
<td>&gt; 5 to 10</td>
<td>571 (24.5)</td>
<td>585 (24.9)</td>
<td>590 (25.2)</td>
</tr>
<tr>
<td>&gt; 10 YEARS!!</td>
<td>1339 (57.4)</td>
<td>1354 (57.7)</td>
<td>1318 (56.3)</td>
</tr>
<tr>
<td><strong>Glucose-lowering medication</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>1734 (74.3)</td>
<td>1729 (73.7)</td>
<td>1730 (73.9)</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>992 (42.5)</td>
<td>985 (42.0)</td>
<td>1029 (43.9)</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>101 (4.3)</td>
<td>96 (4.1)</td>
<td>102 (4.4)</td>
</tr>
<tr>
<td><strong>Insulin</strong></td>
<td>1135 (48.6)</td>
<td>1132 (48.3)</td>
<td>1120 (47.8)</td>
</tr>
<tr>
<td><strong>Mean daily dose, U†</strong></td>
<td>65 (50.6)</td>
<td>65 (47.9)</td>
<td>66 (48.9)</td>
</tr>
</tbody>
</table>

*Medication taken alone or in combination

†Placebo, n = 1135; empagliflozin 10 mg, n = 1132; empagliflozin 25 mg, n = 1120

Data are n (%) or mean (SD) in patients treated with ≥ 1 dose of study drug.

## EMPA-REG: Baseline Characteristics CVD

Data are n (%) in patients treated with ≥ 1 dose of study drug.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 2333)</th>
<th>Empagliflozin 10 mg (n = 2345)</th>
<th>Empagliflozin 25 mg (n = 2342)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CV risk factor, no. (%)</td>
<td>2307 (98.9)</td>
<td>2333 (99.5)</td>
<td>2324 (99.2)</td>
</tr>
<tr>
<td>Coronary artery disease, no. (%)</td>
<td>1763 (75.6)</td>
<td>1782 (76.0)</td>
<td>1763 (75.3)</td>
</tr>
<tr>
<td>Multi-vessel coronary artery disease, no. (%)</td>
<td>1100 (47.1)</td>
<td>1078 (46.0)</td>
<td>1101 (47.0)</td>
</tr>
<tr>
<td>History of MI, no. (%)</td>
<td>1083 (46.4)</td>
<td>1107 (47.2)</td>
<td>1083 (46.2)</td>
</tr>
<tr>
<td>Coronary artery bypass graft, no. (%)</td>
<td>563 (24.1)</td>
<td>594 (25.3)</td>
<td>581 (24.8)</td>
</tr>
<tr>
<td>History of stroke, no. (%)</td>
<td>553 (23.7)</td>
<td>535 (22.8)</td>
<td>549 (23.4)</td>
</tr>
<tr>
<td>Peripheral artery disease, no. (%)</td>
<td>479 (20.5)</td>
<td>465 (19.8)</td>
<td>517 (22.1)</td>
</tr>
<tr>
<td>Single vessel coronary artery disease, no. (%)</td>
<td>238 (10.2)</td>
<td>258 (11.0)</td>
<td>240 (10.2)</td>
</tr>
<tr>
<td>Cardiac failure*, no. (%)</td>
<td>244 (10.5)</td>
<td>240 (10.2)</td>
<td>222 (9.5)</td>
</tr>
</tbody>
</table>

*Based on narrow standardized MedDRA query "cardiac failure."

LEADER: Primary Outcome
CV Death, Nonfatal MI, or Nonfatal Stroke

The primary composite outcome in the time-to-event analysis was the first occurrence of CV death, nonfatal MI, or nonfatal stroke.

The cumulative incidences were estimated with the use of the Kaplan-Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model.

The data analyses were truncated at 54 months, because <10% of the patients had an observation time beyond 54 months.

HR: 0.87 (95% CI, 0.78-0.97)
p<.001 for noninferiority
p=.01 for superiority

CI upper limit <1.3
Liraglutide met the noninferiority criterion (did not increase the risk of CV events vs. placebo) (primary objective)

CI upper limit <1.0
Liraglutide demonstrated superiority (reduced risk for CV events) vs. placebo


The primary composite outcome in the time-to-event analysis was the first occurrence of CV death, nonfatal MI, or nonfatal stroke.
The cumulative incidences were estimated with the use of the Kaplan-Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model.
The data analyses were truncated at 54 months, because <10% of the patients had an observation time beyond 54 months.
LEADER: Patient Population

Majority of LEADER patients Are High Cardiovascular Risk

- Previous CVD: 81.3% (n = 7592)
- No Previous CVD: 18.7% (n = 1748)

N = 9340

CV Outcomes: Semaglutide vs Placebo

N = 3,297

Median f/u: 2.1 yr

Hospitalization for HF: 3.6 vs 3.3%
HR 1.11
(95% CI, 0.77-1.61)

Marso SP, et al. NEJM, 2016; Sept 16
## Comparison of Major Outcome Relative Rates in LEADER, SUSTAIN 6 and EXSCEL Trials

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LEADER</th>
<th>SUSTAIN 6</th>
<th>EXSCEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point MACE</td>
<td>0.87</td>
<td>0.74</td>
<td>0.91</td>
</tr>
<tr>
<td>Nonfatal Stroke</td>
<td>0.89</td>
<td>0.61</td>
<td>0.85</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>0.78</td>
<td>0.98</td>
<td>0.88</td>
</tr>
<tr>
<td>Death any cause</td>
<td>0.85</td>
<td>1.05</td>
<td>0.86</td>
</tr>
<tr>
<td>Hospital Heart Failure</td>
<td>0.87</td>
<td>1.11</td>
<td>0.94</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>0.78</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Retinopathy</td>
<td>1.15</td>
<td>1.76</td>
<td></td>
</tr>
</tbody>
</table>

*Red Color* is statistically significant versus study control group.
At diagnosis, initiate lifestyle management, set A1C target, and initiate pharmacologic therapy based on A1C:

**Dual Therapy**

- Metformin +

**Lifestyle Management**

- Sulfonylurea
- Thiazolidinedione
- DPP-4 inhibitor
- SGLT2 inhibitor
- GLP-1 receptor agonist
- Insulin (basal)

**Triple Therapy**

Lifestyle Management + Metformin + Two Additional Agents

Add third agent based on drug-specific effects and patient factors# (See Table 8.1)

**A1C at target after 3 months of triple therapy?**

- **Yes:** - Monitor A1C every 3–6 months
  - **No:** - Assess medication-taking behavior
  - Consider Combination Injectable Therapy (See Figure 8.2)

**Combination Injectable Therapy**

(See Figure 8.2)
Coronary Heart Disease: Recommendations

Screening

• In asymptomatic patients, routine screening for CAD is not recommended as it does not improve outcomes as long as ASCVD risk factors are treated. A

• Consider investigations for CAD in the presence of:
  – Atypical cardiac symptoms (e.g. unexplained dyspnea, chest discomfort)
  – Signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication or PAD
  – EKG abnormalities (e.g. Q waves). E
Questions from Portland

• How do you respond to questions around these drugs that they are expensive blood pressure medicines?
• The FDA advisory committee was a very close vote for CV approval: 12-11. Do you have any insight into that?
• Real-world A1c efficacy of these products fall short; should the real world CV outcomes also not also be questioned?
• For empagliflozin, the hazard ratios for CV deaths was only statistically significant in Latin America and Asian study sites, but not in Europe and N America. Do you have insight into that?
• How do these best-case drug interventions compare to best-case diet and exercise interventions?
2018 ADA Standards of Care

Note/Disclosure:
ADA/EASD just incorporated
New trial results coming out every few months
New FDA guidance yesterday
**Patient/Disease Features**

- **Risk of hypoglycemia/drug adverse effects**
  - low
  - high
- **Disease Duration**
  - newly diagnosed
  - long-standing
- **Life expectancy**
  - long
  - short
- **Important comorbidities**
  - absent
  - Few/mild
  - severe
- **Established vascular complications**
  - absent
  - Few/mild
  - severe
- **Patient attitude & expected treatment efforts**
  - highly motivated, adherent, excellent self-care capabilities
  - less motivated, nonadherent, poor self-care capabilities
- **Resources & support system**
  - readily available
  - limited

**Glycemic Targets:**
*Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S55-S64*
Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Makarios J. Davies,1,2,* David A. Enright,1,2 Rachel Franks,1,2 Anthony H. Harman,1,2 Cheryl Matthews,1,2,3 Gillian Marzocco1,2,3 Peter Haring1,2,3 Apostolos Taoussis1,2,3* Deborah J. Wilkins1,2,3* John B. Buse1,2
1European Association for the Study of Diabetes and American Diabetes Association 2018

Abstract
The American Diabetes Association and the European Association for the Study of Diabetes convened a panel to update the prior position statements published in 2012 and 2013 on the management of type 2 diabetes in adults. A systematic evaluation of the literature since 2014 informed new recommendations. These include additional focus on lifestyle management and diabetes self-management education and support. For these with obesity, efforts aiming weight loss, including dietary modulation and surgical interventions, are recommended. Strategies to manage hypoglycemia, for patients with clinical cardiovascular disease, apheresis treatment, and omega-3 fatty acids are generally recommended. For patients with chronic kidney disease or chronic heart failure and abnormal cardiac function, an SGLT2 inhibitor with proven benefit is recommended. GLP-1 receptor agonists are generally discouraged. For the first time in this edition, cardiovascular clinical trials are highlighted as a new evidence source has emerged.

Keywords: Cardiovascular disease - Chronic kidney disease - CVD - Glucose-lowering therapy - Guidelines - Heart failure - Hypoglycemia - Polycystic ovary syndrome - Type 2 diabetes mellitus - Weight management

Diabetes Care 2018;41:1-33 https://doi.org/10.2337/dci18-0033

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*These authors contributed equally to this work.
Putting the Patient at the Center of Care
Balancing Risks and Benefits for Personalized Goals

More Stringent Control
- No hypoglycaemia
- Less complexity/polypharmacy
- Lifestyle or metformin only
- Short disease duration
- Long life expectancy
- No CVD

Less Stringent Control
- History of severe hypoglycaemia
- High burden of therapy
- Longer disease duration
- Limited life expectancy
- Extensive co-morbidity
- CVD
DECISION CYCLE FOR PATIENT-CENTRED GLYCAEMIC MANAGEMENT IN TYPE 2 DIABETES

GOALS OF CARE
- Prevent complications
- Optimise quality of life

REVIEW AND AGREE ON MANAGEMENT PLAN

ASSESS KEY PATIENT CHARACTERISTICS

CONSIDER SPECIFIC FACTORS WHICH IMPACT ON CHOICE OF TREATMENT

ONGOING MONITORING AND SUPPORT

IMPLEMENT MANAGEMENT PLAN

AGREE ON MANAGEMENT PLAN

SHARE DECISION-MAKING TO CREATE A MANAGEMENT PLAN
Improving Glycemic Management

• Focus on treatments for glycemic control
  • Behavioral approaches
  • Medications
  • Metabolic surgery

• Addresses increasing complexity of patient centered therapeutic decisions in the context of expanding therapeutic options and new information on benefits and risks
Key Considerations

Patient and Provider Barriers
Lifestyle as Medicine

- Medical Nutrition Therapy
- Physical Activity
Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S73-S85

**Monotherapy**
**Lifestyle Management - Metformin**

Initiate metformin therapy if no contraindications* (See Table 8.1)

**Dual Therapy**
Metformin +

**Lifestyle Management**

**ASCVD? Yes:** - Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and Table 8.1)

**Triple Therapy**
**Lifestyle Management + Metformin + Two Additional Agents**

**Combination Injectable Therapy** (See Figure 8.2)
CENTRAL ILLUSTRATION: Healthy Lifestyle and Cardiovascular Disease (CVD) Events Among Diabetic Patients

<table>
<thead>
<tr>
<th></th>
<th>Intensive Lifestyle</th>
<th>Diabetes Support/Education</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1yr Weight</td>
<td>8.6%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Year 1yr Fitness</td>
<td>20.4%</td>
<td>5%</td>
</tr>
<tr>
<td>HR recovery</td>
<td>P&lt;0.001</td>
<td>--</td>
</tr>
<tr>
<td>A1c &lt;7%</td>
<td>46-73%</td>
<td>45-50%</td>
</tr>
<tr>
<td>Glucose/BP/Cholesterol</td>
<td>10.8-23.6%</td>
<td>9.5-16%</td>
</tr>
<tr>
<td>CAD outcome</td>
<td>153 SNP-prediction unchanged</td>
<td>153 SNP-prediction unchanged</td>
</tr>
<tr>
<td>CKD</td>
<td>0.63 per 100 person-years</td>
<td>0.91 cases per 100 per/yr</td>
</tr>
<tr>
<td>Physical Function Decline</td>
<td>Slowed progression*</td>
<td></td>
</tr>
<tr>
<td>Cognitive Function</td>
<td>Favor ILI</td>
<td></td>
</tr>
<tr>
<td>Fitness</td>
<td>Favor ILI</td>
<td></td>
</tr>
<tr>
<td>Preserve physical HRQoL</td>
<td>Favor ILI</td>
<td></td>
</tr>
<tr>
<td>Clinically significant depression</td>
<td>Favor ILI</td>
<td></td>
</tr>
</tbody>
</table>

Diabetes is usually for life

$1 in 4

30.3 Million

24/7/365

American Diabetes Association.
How to support lifestyle change?

- Providers need to reinforce the use of lifestyle as medicine.
- Messaging needs to be non-judgmental and realistic.
- People with diabetes need a toolkit.
- Use of Diabetes Self Management Education (DSME) and Certified Diabetes Educators (CDE) enhances success.
Background on Behavioral Theory

- Human Behavior is influenced by motivation and ability
- Models vary, but generally identify factors related to motivation and ability:
  - **Motivation:**
    - Cognitive factors
    - Environmental/Social factors
  - **Ability:**
    - Behavioral factors

Bandura, Social Cognitive Theory, 1986
Human behavior is influenced by motivation and ability

Pre-Contemplation
- No; Denial

Contemplation
- Maybe; Ambivalence

Determination/Preparation
- 0–3 Months
- Yes, Let’s Go; Motivated

Action
- 3–6 Months
- Doing It; Go

Maintenance
- Over 6 months
- Living It

Relapse/Recycle
- Ugh!!

Courtesy of A Huebschmann  Fogg Behavior Model, www.behaviormodel.org
Diabetes Self-Management Education and Support (DSMES)

Is available to patients at **critical times (repeated as needed)**

Individualized to the needs of the person, including language and culture

Structured theory-driven written curriculum with supporting materials

Delivered in group or individual settings by trained educators

Promote healthy eating, physical activity, good medication-taking behavior, and increase self-efficacy

Supports person and their family in developing attitudes, beliefs, knowledge and skills to self-manage diabetes

Includes core content and monitoring of patient progress, including health status, quality of life.

Evidence-based
Empathic patient-centered care

Patients with diabetes often live with multiple chronic conditions. Providers & health care systems should prioritise the delivery of empathic, individualised patient-centred care.

To determine what is the best management option for each patient, consider each individual’s

- personal, social and biomedical context,
- his/her values,
- reasons he/she values the available options, and
- relative contribution of each option in terms of benefits, harms, costs and inconveniences.
### 5A’s – Adapted to be DM Specific

| Ask                  | • Ask for permission to discuss **dietary habits and activity**  
<table>
<thead>
<tr>
<th></th>
<th>• Explore readiness for change.</th>
</tr>
</thead>
</table>
| Assess               | • Assess lifestyle habits and history.  
|                      | • Success and failures of prior attempts to alter behavior and perceived barriers for making changes. |
| Advise               | • Advise the patient about the health risks of ‘poor’ lifestyle habits, the benefits of changes, the need for long-term strategy, and treatment options. |
| Agree                | • Agree on realistic expectations, targets, behavioral changes, and specific details of the treatment plan. |
| Arrange/Assist       | • Assist in identifying and addressing barriers; provide resources; assist in finding and consulting with appropriate providers; arrange regular follow up. |

Adapted From Obesity Algorithm®. ©2016-2017 Obesity Medicine Association courtesy of T Halliday.
In this study…

- **45.2%** of individuals with BMI $\geq 25$ had been told they were overweight
- **66.4%** of individuals with BMI $\geq 30$ had been told they were overweight

If patients hear from a **physician or other healthcare professional** that they are overweight, they are…

- ~2.5x more likely to attempt weight loss
- ~6x more likely to perceive themselves as overweight


Courtesy T Halliday
Tools:
Use trustworthy sources
People eat food (not carbohydrate, protein and fat):

Food & Fitness

Eating well-balanced is better care of yourself physical activity, which with diabetes and you eat and your physical diabetes.

Choose MyPlate.gov

Nutrition Facts
Serving Size 1/3 cup (55g)
Servings Per Container About 8

<table>
<thead>
<tr>
<th>Amount Per Serving</th>
<th>% Daily Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calories 230</td>
<td>5%</td>
</tr>
<tr>
<td>Fat 8g</td>
<td>12%</td>
</tr>
<tr>
<td>Saturated Fat 1g</td>
<td>0%</td>
</tr>
<tr>
<td>Trans Fat 0g</td>
<td>0%</td>
</tr>
<tr>
<td>Cholesterol 0mg</td>
<td>0%</td>
</tr>
<tr>
<td>Sodium 160mg</td>
<td>7%</td>
</tr>
<tr>
<td>Total Carbohydrate 57g</td>
<td>16%</td>
</tr>
<tr>
<td>Dietary Fiber 4g</td>
<td></td>
</tr>
<tr>
<td>Sugars 1g</td>
<td></td>
</tr>
<tr>
<td>Protein 3g</td>
<td></td>
</tr>
</tbody>
</table>

Vitamin A 10%
Vitamin C 8%
Calcium 20%
Iron 4%

Amount per serving
Calories 230

*Percent Daily Values are based on a 2,000 calorie diet. Your daily value may be higher or lower depending on your calorie needs.

Food

Recipes
Eating healthful meals is an essential part of managing diabetes. All of our

Fitness
Manage or prevent type 2 diabetes by getting and staying active.

GO FURTHER with FOOD

NATIONAL NUTRITION MONTH® 2018
Learn More
Diet and Exercise are the cornerstones of successful diabetes management (on or off medication)

People with diabetes and the providers need skills to implement sustainable lifestyle intervention

Provider silence on lifestyle is unacceptable

Patient support in the form of diabetes self management education is crucial (early and often)

If at first you don’t succeed-try something else
Lifestyle can add or subtract medications

Still.....Diabetes is progressive
UKPDS: Progressive Hyperglycemia Secondary to Beta-Cell Failure

NOT your fault!

“Intensive” Monotherapy

Conventional

Sulfonylurea

Metformin

HbA1c (%)

Beta-Cell Function (%)

Years from Randomization


Clinical Inertia

Clinical inertia: failure of healthcare providers to initiate or intensify therapy when indicated, due to:

- overestimation of care provided
- use of “soft” reasons to avoid intensification of therapy
- lack of education, training, and practice organization aimed at achieving therapeutic goals
- Reusch addition: health care system barriers adding burden to providers to intensify therapy
How are we doing?
Cardiovascular (CV) Risk Factor Targets and CV Disease Event Risk in Diabetes: We are not getting the job done

Percent at target levels for any one, two, or all three factors among the 2016 persons with diabetes:

<table>
<thead>
<tr>
<th></th>
<th>Any 1 of 3</th>
<th>Any 2 of 3</th>
<th>3 of 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent</td>
<td>41.1%</td>
<td>26.5%</td>
<td>7.2%</td>
</tr>
</tbody>
</table>

Percent CVD risk reduction for being at target level among the 2016 persons with diabetes for each of the measures:

<table>
<thead>
<tr>
<th>Measure</th>
<th>Blood pressure</th>
<th>LDL-C</th>
<th>HBA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent</td>
<td>17%</td>
<td>33%</td>
<td>37%</td>
</tr>
</tbody>
</table>

Percent lower adjusted risk of CVD events with one, two, or three risk factors at target level:

<table>
<thead>
<tr>
<th></th>
<th>Any 1 of 3</th>
<th>Any 2 of 3</th>
<th>3 of 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent</td>
<td>36%</td>
<td>52%</td>
<td>62%</td>
</tr>
</tbody>
</table>

GOALS OF CARE

- Prevent complications
- Optimize quality of life

REVIEW AND AGREE ON MANAGEMENT PLAN
- Review management plan
- Mutual agreement on changes
- Ensure agreed modification of therapy is implemented in a timely fashion to avoid clinical inertia
- Decision cycle undertaken regularly (at least once/twice a year)

ONGOING MONITORING AND SUPPORT INCLUDING:
- Emotional well-being
- Check tolerability of medication
- Monitor glycemic status
- Biofeedback including SMBG, weight, step count, HbA1c, BP, lipids

IMPLEMENT MANAGEMENT PLAN
- Patients not meeting goals generally should be seen at least every 3 months as long as progress is being made; more frequent contact initially is often desirable for DSMES

ASSESS KEY PATIENT CHARACTERISTICS
- Current lifestyle
- Comorbidities i.e. ASCVD, CKD, HF
- Clinical characteristics i.e. age, HbA1c, weight
- Issues such as motivation and depression
- Cultural and socio-economic context

CONSIDER SPECIFIC FACTORS WHICH IMPACT CHOICE OF TREATMENT
- Individualised HbA1c target
- Impact on weight and hypoglycaemia
- Side effect profile of medication
- Complexity of regimen i.e. frequency, mode of administration
- Choose regimen to optimise adherence and persistence
- Access, cost and availability of medication

SHARED DECISION-MAKING TO CREATE A MANAGEMENT PLAN
- Involves an educated and informed patient (and their family/caregiver)
- Seeks patient preferences
- Effective consultation includes motivational interviewing, goal setting and shared decision-making
- Empowers the patient
- Ensures access to DSMES

AGREE ON MANAGEMENT PLAN
- Specify SMART goals:
  - Specific
  - Measurable
  - Achievable
  - Realistic
  - Time limited

ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose
Diabetes is VERY Demanding
Persistence and medication adherence

Mean medication adherence rate ≈ 75%, average proportion of patients adherent to medication < 70%.

Adherence slightly varies between orals vs injectable therapy and individual classes

Discontinuation rates range from 10% to 60% (both in observational studies and in clinical trials)
• Traditional CVD risk factor modification remains the top priority for CVD prevention
• Healthy diet, increased physical activity and decreased sedentary activity are all effective THERAPY
• The primary goal for antihyperglycemic agents is to improve glucose control; combination therapy is often needed
• Polypharmacy, cost, durability, adherence and cost effectiveness must be considered*
• Studies demonstrating dual efficacy of antihyperglycemic agents on glucose and CVD/CHF change the landscape ONLY in people with high CHD risk or established CHD
• No data address the person with T2D and CHD on metformin with glucose at goal
Where are the gaps?

• **Underlying biology:**
  – The mechanisms for the interaction between GLP-1RA and SGLT2I and decreased CVD and CHF risk need clarification

• **Diabetes is a progressive disease:**
  – The timing and physiological context in which these drugs are administered needs to be tested (TZDs/Estrogen)
  – No data demonstrating a role for these agent in primary prevention despite theoretical benefit whereas lifestyle change confers consistent benefits for primary prevention

• **Health care delivery:**
  – Chronic disease with social stigma
  – Glucose management is difficult in short patient visit
  – PCPs and people with DM need support when starting GLP1 RA and SGLT2 inhibitors
  – Reallocation of the $327 Billion / 1 in 4 US Health Care dollars
Consensus and Harmonization

ADA, AACE, Endocrine Society, AAFP scheduling discussion about Glycemic Targets

ACC Expert Consensus Decision Pathways on Novel Pathways for Cardiovascular Risk Reduction in Patients with Type 2 Diabetes

Diabetes Cardiovascular (DCV) Initiative
Thank you!

Questions?
Key points to emphasize

Update informed by evidence generated in the past 2 years

Greater focus on lifestyle interventions, with increased emphasis on weight loss and obesity management, including metabolic surgery

Greater focus on patient related issues and self-management which have a major impact on success of any pharmacological interventions

Preferred choices of glucose-lowering agents driven by new evidence from CVOTs and consideration of areas of major clinical need (for example weight and risk of hypoglycaemia)

GLP-1 RAs are preferred to insulin as first injectable