How to Use the American Diabetes Association’s Type 2 Diabetes Algorithm

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American Diabetes Association

Disclosures of Interest

No disclosures to report
GLOBAL PREVALENCE EXPECTED TO INCREASE 48% BY 2045

2017 Statistics:
- Over 11% prevalence in US
- Type 2 diabetes accounts for 90 to 95% of all diabetes cases
- 325 Million globally at risk
- 4 Million deaths attributable to diabetes
- $727 billion (USD) in health expenditure

Multiple, Complex Pathophysiological Abnormalities in T2DM

Adapted from: Inzucchi SE, Sherwin RS in: Cecil Medicine 2011

Therapeutic Advances Over Past 20 Years

Update on Latest Treatment Recommendations

➢ Appropriate glycemic target?
  – Considering the “company it keeps!”

➢ Clinical approach to arrive at the target?
  – Concept of “metabolic memory”
  – Overcoming clinical inertia

➢ CV consequences of diabetes?

➢ New Algorithm to achieve individualized goals.

American Diabetes Association.
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Consensus Statement for the Management of Type 2 Diabetes

STEP 1  
*At diagnosis: Lifestyle + MET* 

If A1C ≥7% 

Advance to STEP 2 Therapies

## A Broad View of Glycemia and Complications

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvascular</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
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<tr>
<td>DCCT/EDIC</td>
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<tr>
<td>ACCORD</td>
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<td>VADT</td>
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</tr>
</tbody>
</table>

HbA1C Goal is not “One-size-fits-all”

More Stringent (as close to 6% as possible)

ADA < 7%
AACE ≤ 6.5%

Less Stringent (< 8%)

No broad agreement on A1C targets

American Association of Clinical Endocrinologists < 6.5%
American Diabetes Association < 7%
American College of Physicians < 8%

Hemoglobin A₁c Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians

Doctors’ Group Issues Controversial Advice for Type-2 Diabetes

American College of Physicians ups A1c limit to 8%

TREATMENTS

Major Medical Associations Feud Over Diabetes Guidelines

March 5, 2018 - 5:01 PM ET

Ann Intern Med. 6 March 2018

Annals of Internal Medicine

Guidelines Versus Guidelines: What’s Best for the Patient?

A1C Targets Should Be Personalized to Maximize Benefits While Limiting Risks

Diabetes Care 2018;41:1121–1124 | https://doi.org/10.2337/dc18-0018

Medical News & Perspectives

For Patients With Type 2 Diabetes, What’s the Best Target Hemoglobin A₁c?

JAMA  Published online May 30, 2018
Update on Latest Treatment Recommendations

- Appropriate glycemic target?
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Glycemic Control Reduces Long-Term Risk of Macrovascular Complications: DCCT-EDIC

- Any CV outcome: 42% Risk Reduction
  \[ P = 0.02 \]

- Nonfatal MI, stroke, or death from CVD: 57% Risk Reduction
  \[ P = 0.02 \]

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>Intensive</th>
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<tbody>
<tr>
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<tr>
<td>20</td>
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</tr>
</tbody>
</table>

DCCT = Diabetes Control and Complications Trial.
Steno-2 Follow-Up

Conventional therapy

Intensive therapy

Glycated Hemoglobin

Systolic Blood Pressure

LDL Cholesterol

Diastolic Blood Pressure

Years

Glycated Hemoglobin (%)

LDL Cholesterol (mg/dl)

Systolic Blood Pressure (mm Hg)

Diastolic Blood Pressure (mm Hg)

Years

Steno-2 Follow-Up Years: Cardiovascular Events

Metabolic Memory?

Cumulative Incidence of Death

Cumulative Incidence of Any Cardiovascular Event

Metabolic Memory: ACCORD Follow-on Study

Persistent Effects of Intensive Glycemic Control on Retinopathy in Type 2 Diabetes in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Follow-On Study

“Metabolic memory” and “legacy effect”

The ADA recommends that a reasonable A1C goal for many nonpregnant adults with type 2 diabetes is less than 7 percent based on the available evidence to date and incorporated into ADA’s Standards of Care.

Big Picture Messages

• Type 1 and type 2 diabetes: *early* meticulous glucose control can prevent microvascular and neuropathic complications

• Type 1 and type 2 diabetes: *early* meticulous glucose control appears to prevent CVD many years later (“metabolic memory” and “legacy effect”)
Overcoming Therapeutic Intertia

Published Conceptual Approach

HbA\textsubscript{1c} Goal

- Mean HbA\textsubscript{1c} of patients

OAD = oral anti-hyperglycemic agent.

Overcoming Therapeutic Intertia

Early combination approach

OAD = oral anti-hyperglycaemic drug.
Update on Latest Treatment Recommendations

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American Diabetes Association.

Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes

“…data from 1998 to 2014 showed marked reductions in mortality and in the incidence of cardiovascular complications among adults with either type 1 diabetes or type 2 diabetes”.

“There remains a substantial excess overall rate of all outcomes analyzed among persons with either type 1 diabetes or type 2 diabetes as compared with the general population.”

Diabetes & Risk of Heart Failure Hosp/Death

HF rEF: adjusted HR 1.60
95% CI 1.44–1.77; p<0.0001

HF pEF: adjusted HR 2.0
95% CI 1.70–2.36; p<0.0001

MacDonald et al. Eur Heart J 2008;29:1377-85

Cardiovascular Outcomes Trials in Type 2 Diabetes: Where Do We Go From Here? Reflections From a Diabetes Care Editors’ Expert Forum

Diabetes Care 2018;41:14–31 | https://doi.org/10.2337/dc17-0057

William T. Cefalu,1 Sanjay Kaul,2 Hertzel C. Gerstein,3 Rury R. Holman,4 Bernard Zinman,5 Jay S. Skyler,6 Jennifer B. Green,7 John B. Buse,8 Silvio E. Inzucchi,9 Lawrence A. Leiter,10 Itamar Raz,11 Julio Rosenstock,12 and Matthew C. Riddle13
Update on Latest Treatment Recommendations

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American Diabetes Association.
Putting the Patient at the Center of Care

“Optimize quality of life”

Figure 1

DEcision cycle for patient-centred glycaemic management in type 2 diabetes

American Diabetes Association.
Decision cycle for patient-centered glycemic management in type 2 diabetes.

**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)

**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 socioeconomic context

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

**SHARE DECISION MAKING TO CREATE A MANAGEMENT PLAN**
- Involves an educated and informed patient (and their family/carer)
- 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

**ASSESS SMART GOALS CHOOSE THE COURSE OF TREATMENT**
- Individualized HbA1c target
- Impact on weight and hypoglycemia
- Side effect profile of medication
- Complexity of regimen, i.e., frequency, mode of administration
- Choose regimen to optimize adherence and persistence
- Access, cost, and availability of medication

**AMERICAN DIABETES ASSOCIATION**
Standards of Medical Care in Diabetes 2019. Diabetes Care 2019;42(Suppl. 1):S34–S45
Empathic patient-centered care

- Patients with diabetes often live with multiple chronic conditions
- Providers & health care systems should prioritize the delivery of empathic, individualized patient-centered 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.

Decision cycle for patient-centered glycemic management in type 2 diabetes.

ASDOD = American Society for Diabetes and Obesity
DR = Diabetes Risk
HD = Heart Health
ESM = Education and Support
ISMP = Diabetes Self-Monitoring and Control

Decision cycle for patient-centered glycemic management in type 2 diabetes.

Shared decision making in type 2 diabetes

SDM can improve
– decision quality
– patient knowledge
– patient risk perception

Ethical imperative for support of patients’ autonomy
Use of Empowering Language.

Five key consensus recommendations for language use:

1. Use language that is neutral, nonjudgmental, and based on facts, actions, or physiology/biology;
2. Use language that is free from stigma;
3. Use language that is strength based, respectful, and inclusive and that imparts hope;
4. Use language that fosters collaboration between patients and providers;
5. Use language that is person centered (e.g., “person with diabetes” is preferred over “diabetic”).

Diabetes Self-Management Education and Support (DSMES)

- Is available to patients at critical times
- 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
Decision cycle for patient-centered glycemic management in type 2 diabetes.

Glucose Lowering Drug Categories

- Sulfonylureas
- Metformin
- Acarbose
- Meglitinides
- Insulin
- TZDs
- DPP4 inhibitors
- GLP-1 receptor agonists
- SGLT-2 inhibitors
- Other drugs
  - Colesevelam
  - Bromocriptine
  - Pramlintide

Foundational therapy is metformin and comprehensive lifestyle management (including weight management and physical activity)
Step 1: Assess cardiovascular disease
Presence of cardiovascular disease is compelling indication

If ASCVD Predominates:

**GLP-1 receptor** agonist with proven cardiovascular benefit
- Liraglutide > semaglutide > exenatide LAR

**SGLT2 inhibitor** with proven cardiovascular benefit
- Empagliflozin > canagliflozin
LEADER: Kaplan–Meier Estimates of Time to First MACE
Primary MACE: Stratified By Vascular Territory

- Kaplan–Meier estimates (based on number of vascular territories involved at baseline) of time to first primary MACE (composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke); HRs and 95% CIs are based on Cox regression analyses.

GLP1RA CVOTs: Meta-Analysis
Bethel et al. Lancet 2018; 6:105

<table>
<thead>
<tr>
<th>GLP-1 receptor agonist</th>
<th>Placebo</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIXA 400/3034 (13%)</td>
<td>392/3034 (13%)</td>
<td>1.02 (0.89-1.17)</td>
<td>0.776</td>
</tr>
<tr>
<td>LEADER 608/4668 (13%)</td>
<td>694/4672 (15%)</td>
<td>0.87 (0.78-0.97)</td>
<td>0.015</td>
</tr>
<tr>
<td>SUSTAIN 6 108/1648 (7%)</td>
<td>146/1649 (9%)</td>
<td>0.74 (0.65-0.85)</td>
<td>0.016</td>
</tr>
<tr>
<td>EXSCEL 839/7356 (11%)</td>
<td>905/7396 (12%)</td>
<td>0.91 (0.83-1.00)</td>
<td>0.061</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.90 (0.82-0.99)</td>
<td>0.033</td>
</tr>
</tbody>
</table>

Test for heterogeneity: p=0.11, I²=50%

<table>
<thead>
<tr>
<th>Mortality</th>
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<tbody>
<tr>
<td>ELIXA 211/3034 (7%)</td>
</tr>
<tr>
<td>LEADER 381/4668 (8%)</td>
</tr>
<tr>
<td>SUSTAIN 6 62/1648 (4%)</td>
</tr>
<tr>
<td>EXSCEL 507/7356 (7%)</td>
</tr>
<tr>
<td>Overall</td>
</tr>
</tbody>
</table>

Test for heterogeneity: p=0.63, I²=0%

© HCG 2015
© HCG 2018

Bethel et al. Lancet D&E 2017; Online

3 Point MACE
Mortality
### GLP1RA CVOTs: Meta-Analysis
Bethel et al. Lancet 2018; 6:105

<table>
<thead>
<tr>
<th></th>
<th>GLP-1 receptor agonist</th>
<th>Placebo</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td><strong>Severe Hypo</strong></td>
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<tr>
<td>ELIXA</td>
<td>14/3034 (&lt;1%)</td>
<td>24/3034 (1%)</td>
<td>0.58 (0.30-1.13)</td>
<td>0.11</td>
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<tr>
<td>LEADER</td>
<td>114/4668 (2%)</td>
<td>153/4672 (3%)</td>
<td>0.74 (0.58-0.95)</td>
<td>0.016</td>
</tr>
<tr>
<td>SUSTAIN 6</td>
<td>369/1648 (22%)</td>
<td>350/1649 (21%)</td>
<td>1.07 (0.91-1.26)</td>
<td>0.42</td>
</tr>
<tr>
<td>EXSCEL</td>
<td>247/7356 (3%)</td>
<td>219/7396 (3%)</td>
<td>1.14 (0.95-1.37)</td>
<td>0.17</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>0.93 (0.74-1.18)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

*Test for heterogeneity: p=0.64, I²=0%*

<table>
<thead>
<tr>
<th></th>
<th>GLP-1 receptor agonist</th>
<th>Placebo</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pancreatitis</strong></td>
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<tr>
<td>ELIXA</td>
<td>5/3034 (&lt;1%)</td>
<td>8/3034 (1%)</td>
<td>0.62 (0.20-1.91)</td>
<td>0.41</td>
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<tr>
<td>LEADER</td>
<td>18/4668 (&lt;1%)</td>
<td>23/4672 (1%)</td>
<td>0.78 (0.42-1.45)</td>
<td>0.44</td>
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<tr>
<td>SUSTAIN 6</td>
<td>9/1648 (1%)</td>
<td>12/1649 (1%)</td>
<td>0.75 (0.32-1.78)</td>
<td>0.51</td>
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<tr>
<td>EXSCEL</td>
<td>26/7356 (&lt;1%)</td>
<td>22/7396 (1%)</td>
<td>1.19 (0.67-2.10)</td>
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<tr>
<td>Overall</td>
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<td>0.90 (0.63-1.28)</td>
<td>0.54</td>
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*Test for heterogeneity: p=0.06, I²=60%*

### SGLT2i CVOTs: Meta-Analysis
Zelniker et al. Lancet 2018; Online

<table>
<thead>
<tr>
<th>Drug</th>
<th>EMPA-REG OUTCOME&lt;sup&gt;k&lt;/sup&gt;</th>
<th>CANVAS Program&lt;sup&gt;j&lt;/sup&gt;</th>
<th>DECLARE-TIMI 58&lt;sup&gt;i&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td>Empagliflozin</td>
<td>Canagliflozin</td>
<td>Dapagliflozin</td>
</tr>
<tr>
<td>Doses analysed</td>
<td>10 mg, 25 mg (once daily)</td>
<td>100 mg, 300 mg (once daily)</td>
<td>10 mg (once daily)</td>
</tr>
<tr>
<td>Median follow-up time, years</td>
<td>3.1</td>
<td>2.4</td>
<td>4.2</td>
</tr>
<tr>
<td>Trial participants</td>
<td>7020</td>
<td>10142</td>
<td>17160</td>
</tr>
<tr>
<td>Age, mean</td>
<td>63.1</td>
<td>63.3</td>
<td>63.9</td>
</tr>
<tr>
<td>Women</td>
<td>2004 (28.5%)</td>
<td>3533 (35.8%)</td>
<td>6422 (37.4%)</td>
</tr>
<tr>
<td><strong>Patients with established atherosclerotic cardiovascular disease</strong></td>
<td>7020 (100%)</td>
<td>6656 (65.6%)</td>
<td>6974 (40.6%)</td>
</tr>
<tr>
<td><strong>Patients with a history of heart failure</strong></td>
<td>706 (10.1%)</td>
<td>1461 (14.4%)</td>
<td>1724 (10.0%)</td>
</tr>
<tr>
<td>Patients with eGFR &lt;60 ml/min per 1.73 m²</td>
<td>1819 (25.9%)</td>
<td>2039 (20.1%)</td>
<td>1265 (7.4%)</td>
</tr>
</tbody>
</table>
### SGLT2i CVOTs: Meta-Analysis

**Zelniker et al. Lancet 2018; Online**

#### MI/Stroke, or CV Death

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Events</th>
<th>Treatment Events per 1000 pt-yrs</th>
<th>Placebo Events per 1000 pt-yrs</th>
<th>Weights (%)</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>7020</td>
<td>772</td>
<td>37.4</td>
<td>43.9</td>
<td>23.2</td>
<td>0.86 [0.74, 0.99]</td>
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<tr>
<td>CANVAS Program</td>
<td>10142</td>
<td>1011</td>
<td>26.9</td>
<td>31.5</td>
<td>29.7</td>
<td>0.86 [0.75, 0.97]</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>17160</td>
<td>1559</td>
<td>22.6</td>
<td>24.2</td>
<td>47.2</td>
<td>0.93 [0.84, 1.03]</td>
</tr>
</tbody>
</table>

FE Model (P-value = 0.0014)

\$Q$ statistic = 1.20, p=0.55, $I^2$ = 0%

---

### SGLT2i CVOTs: Meta-Analysis – Side Effects

**Zelniker et al. Lancet 2018; Online**

#### Amputations

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Events</th>
<th>Treatment Events per 1000 pt-yrs</th>
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<th>Weights (%)</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>7020</td>
<td>131</td>
<td>6.5</td>
<td>6.5</td>
<td>24.0</td>
<td>1.01 [0.70, 1.44]</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>10142</td>
<td>187</td>
<td>6.3</td>
<td>3.4</td>
<td>28.0</td>
<td>1.97 [1.41, 2.75]</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>17143</td>
<td>236</td>
<td>3.6</td>
<td>3.3</td>
<td>47.9</td>
<td>1.09 [0.84, 1.40]</td>
</tr>
</tbody>
</table>

FE Model (P-value = 0.0096)

\$Q$ statistic = 9.56, p=0.0084, $I^2$ = 79.1%
### Fractures

<table>
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<tr>
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<th>Placebo Events per 1000 pt-yrs</th>
<th>Weights (%)</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>7020</td>
<td>270</td>
<td>NA</td>
<td>NA</td>
<td>17.7</td>
<td>0.98 [0.76, 1.25]</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>10142</td>
<td>NA</td>
<td>15.4</td>
<td>11.9</td>
<td>18.2</td>
<td>1.55 [1.21, 1.97]</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>17143</td>
<td>897</td>
<td>13.6</td>
<td>13.2</td>
<td>64.1</td>
<td>1.04 [0.91, 1.18]</td>
</tr>
</tbody>
</table>

FE Model (P-value = 0.0564)

Q statistic = 9.16, p=0.0102, I² = 78.2%

### Diabetic Ketoacidosis

<table>
<thead>
<tr>
<th>Study</th>
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<th>Events</th>
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<th>Placebo Events per 1000 pt-yrs</th>
<th>Weights (%)</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>7020</td>
<td>5</td>
<td>0.1</td>
<td>&lt;0.1</td>
<td>6.6</td>
<td>1.99 [0.22, 17.80]</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>10142</td>
<td>18</td>
<td>0.6</td>
<td>0.3</td>
<td>25.2</td>
<td>2.33 [0.76, 7.17]</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>17143</td>
<td>39</td>
<td>0.9</td>
<td>0.4</td>
<td>68.2</td>
<td>2.18 [1.10, 4.30]</td>
</tr>
</tbody>
</table>

FE Model (P-value = 0.0060)

Q statistic = 0.02, p=0.99, I² = 0%
CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED HF OR CKD

EMPÁ-REG
Hospitalization for heart failure, secondary outcome

NNT: 71 over 3 years

SGLT2i CVOTs: Meta-Analysis – CV Outcomes
Zelniker et al. Lancet 2018; Online

Heart Failure Hospitalization

<table>
<thead>
<tr>
<th>Treatment Events per 1000 pt-yrs</th>
<th>Placebo Events per 1000 pt-yrs</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME</td>
<td></td>
<td>0.65 [0.50, 0.85]</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td></td>
<td>0.67 [0.52, 0.87]</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td></td>
<td>0.73 [0.61, 0.88]</td>
</tr>
</tbody>
</table>

FE Model (P-value <0.0001)

Q statistic = 0.60, p=0.74, I²= 0%

EMPA-REG
Time to first renal event (secondary outcome)
Doubling of the serum creatinine level, the initiation of renal-replacement therapy, or death from renal disease

HR=0.54*, 95% CI: 0.40;0.75
p<0.001
LEADER

Time to first renal event (secondary outcome)
Macroalbuminuria, doubling of serum creatinine, ESRD, renal death

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 are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; ESRD: end-stage renal disease; HR: hazard ratio.


SGLT2i CVOTs: Meta-Analysis – Renal
Zelniker et al. Lancet 2018; Online

<table>
<thead>
<tr>
<th>Renal F[1]/ESRD</th>
<th>Patients</th>
<th>Events</th>
<th>Treatment Events per 1000 pt-yrs</th>
<th>Placebo Events per 1000 pt-yrs</th>
<th>Weights (%)</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>7020</td>
<td>152</td>
<td>6.3</td>
<td>11.5</td>
<td>20.9</td>
<td>0.54 [0.40, 0.75]</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>10142</td>
<td>249</td>
<td>5.5</td>
<td>9.0</td>
<td>34.0</td>
<td>0.60 [0.47, 0.77]</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>17160</td>
<td>365</td>
<td>3.7</td>
<td>7.0</td>
<td>45.1</td>
<td>0.53 [0.43, 0.66]</td>
</tr>
</tbody>
</table>

FE Model (P-value <0.0001)

0.55 [0.48, 0.64]

Q statistic = 0.59, p=0.74, I²= 0%
HEART FAILURE: Hospitalization for heart failure was reduced consistently with SGLT2-i in two trials but was a secondary outcome.

CHRONIC KIDNEY DISEASE: For patients with type 2 diabetes and CKD, with or without cardiovascular disease, consider the use of an SGLT2 inhibitor shown to reduce CKD progression or...

.....if contraindicated or not preferred, a GLP-1 receptor agonist shown to reduce CKD progression

Among patients with ASCVD in whom HF coexists or is of concern, SGLT2 inhibitor are recommended

Rationale: Patients with T2D are at increased risk for heart failure with reduced or preserved ejection fraction.

Significant, consistent reductions in hospitalization for heart failure have been seen in SGLT2 inhibitor trials.

Caveat: trials were not designed to adjudicate heart failure.

Majority of patients did not have clinical heart failure at baseline.
For SGLT2-i adequate eGFR differs between countries and compounds.

SGLT2-i are registered as glucose-lowering agents to be started if eGFR > 45-60 ml/min/1.73m² and stopped at eGFR 45-60, as glucose-lowering effect declines with eGFR.

SGLT2-i CVOTs included patients with eGFR > 30, and there were no excess adverse events in subjects with eGFR < 60.

For GLP-1 RA gastrointestinal side effects increase with declining renal function are not recommended in end-stage renal disease due to limited experience.

American Diabetes Association.

### SGLT2i CVOTs: Meta-Analysis – Role of eGFR

Zelniker et al. Lancet 2018; Online

<table>
<thead>
<tr>
<th>eGFR</th>
<th>↓ Renal Fⁿ, ESRD or Renal Death</th>
<th>Heart Failure Hospitalization</th>
<th>MI, Stroke, or CV Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60</td>
<td>0.67 (0.51, 0.89)</td>
<td>0.60 (0.47, 0.77)</td>
<td>0.82 (0.70, 0.95)</td>
</tr>
<tr>
<td>60-89</td>
<td>0.56 (0.46, 0.70)</td>
<td>0.69 (0.57, 0.83)</td>
<td>0.91 (0.82, 1.00)</td>
</tr>
<tr>
<td>&gt; 90</td>
<td>0.44 (0.32, 0.59)</td>
<td>0.88 (0.68, 1.13)</td>
<td>0.94 (0.82, 1.07)</td>
</tr>
</tbody>
</table>

| P Trend | 0.026                      | 0.007                      | 0.2                      |

As eGFR Falls... Less effective More effective More effective
CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ASCVD OR CKD

**ASCVD PREDOMINATES**

- Either/Or
  - GLP-1 RA with proven CVD benefit
  - SGLT2i with proven CVD benefit, if eGFR adequate

If HbA1c above target:
  - If SGLT2i not tolerated or contraindicated or if eGFR less than adequate:
    - Add GLP-1 RA with proven CVD benefit

**HF OR CKD PREDOMINATES**

- Preferably SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate

If HbA1c above target:
  - Avoid TZD in the setting of HF
  - Choose agents demonstrating CV safety:
    - Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
    - DPP-4i if not on GLP-1 RA
    - Basal insulin
    - TZD
    - SU

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### Summarizing the Approach to Management

**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

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Recommendations

In most patients who need the greater glucose-lowering effect of an injectable medication, glucagon-like peptide 1 receptor agonists are preferred to insulin. B

Intensification of treatment for patients with type 2 diabetes not meeting treatment goals should not be delayed. B

The medication regimen should be reevaluated at regular intervals (every 3–6 months) and adjusted as needed to incorporate new patient factors. E
New Onset Patient With Type 2 DM

53-year-old male patient, a college teacher, recently diagnosed with type 2 diabetes during a routine physical. The HbA1c was 7.1 %. His BMI is 32 kg/m2.

He is moderately active and walks approx. 3 miles a day 3 to 4 days a week.

Renal function is normal (estimated glomerular filtration rate [eGFR] of 79 mL/min/1.73 m2). Microalbumin was normal.

He has mild dyslipidemia controlled with a statin and hypertension controlled with an angiotensin II receptor blocker (blood pressure ≤140/90 mm Hg).

Eye exam normal, rest of physical is normal with exception of central obesity.

He questions whether medication is appropriate and really wants to lose weight, but without success.

Metformin Failure

A 65-year-old female patient with 8-year history of T2DM presents with an HbA1c of 7.3 % despite receiving metformin (2000 mg/d) for the last 12 months. Her BMI is 31 kg/m2.

Blood pressure is at target on ACE-I, LDL < 70 mg/dl on statin.

She is asymptomatic, normal renal and hepatic function. FBG: 150-200, mg/dl

Eye exam normal, Central obesity present, diminished sensation to pinprick noted in lower extremities.
Failure of Metformin and DPP-4 Inhibitor

67-year-old male patient with a 10-year history of T2DM presents with an HbA1c of 9.0% despite receiving metformin (2000 mg/d) plus a DPP-4 inhibitor for the last 12 months. His BMI is 37 kg/m2.

Renal function (estimated glomerular filtration rate [eGFR] of 59 mL/min/1.73 m2). ACR was 150 µg albumin/mg creatinine.

He has dyslipidemia (LDL of 120 mg/dl) on low dose statin and hypertension (145/90) while on an angiotensin II receptor blocker and HCTZ.

He has a history of MI 5 years ago. He is not active and complains of fatigue and tiredness during afternoon walks. So, he curtails his walks.

He remains concerned with hypoglycemia, and on initial discussion, desires to avoid insulin.

Type 2 DM, Poorly Controlled, Limited Resources

45-year old male works part time in odd jobs and as a waiter. Married and one child. Diagnosed 2 years ago, currently on metformin 1000 mg BID.

Hypertension history, but on ACE-I with good control, BP < 130/80 mmHg.
No known history of CAD.

BMI = 31, Cr 1.0, AST 29, ALT 30

No medical insurance and does not qualify for Medicaid. Due to resources, only self monitors home blood glucose twice weekly.

A1c 8.5%
Type 2 DM, Elderly, Visually impaired

80-year old retired librarian, type 2 DM for 17 years.

Hypertensive on ACE-I (BP 150/95 mmHg). LDL 110 mg/dl on moderate dose statin. Past history of angioplasty, MI approx. ten years ago, eGFR 44 mL/min/1.73 m², AST/ALT 28/31.

The patient lives alone in a senior retirement community and uses a walker. She eats dinner in community dining room and prepares breakfast and lunch herself.

Has decreased vision and past laser surgery and current vision is 20/100. Currently on metformin 500 mg BID, She take 35 units of Glargine at night.

A1c = 8.6%

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Summary of Approach

➢ Consider the presence or absence of ASCVD, CKD and HF

Start with metformin if tolerated, then:

➢ In patients with ASCVD a GLP-1 RA or SGLT2-i is recommended
➢ In patients with ASCVD and HF SGLT2-i is recommended
➢ In patients with CKD, with or without ASCVD consider an SGLT2-i

➢ Agents with proven benefit are preferred
➢ ASCVD, CKD and HF affects choice of additional glucose lowering medication

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Take Away Messages

➢ We have an incredible arsenal of medications and new options at our disposal

➢ Decisions on strategy and needs to be patient centered

➢ We are entering a new era where all co-morbidities (ASCVD, HF, CKD) needs to be considered

➢ The time is now for now for individualizing goals for the patient and recommending evidenced based strategies

Thanks!!!