Individualizing Type 2 Diabetes Management

Cynthia Gerstenlauer, ANP-BC, GCNS-BC, CDE, CCD
Harsh Statistics

- 30.3 million (9.4% of population) in US had DM in 2015
- ~7.2 million (23.8%) are undiagnosed
- The percent of population with DM increases with age to 25.2% >65 years
- 57 million in US have pre-diabetes (18.8% of population)
- 5-10% with Type 1 diabetes
- One in every 500 children/adolescents
The Burden of Diabetes in Michigan

1,087,000 people or 12.9% of the adult population have diabetes.

2,741,000 people or 37% of the adult population have prediabetes.

Every year 46,000 people are diagnosed with diabetes.

The serious complications include heart disease, stroke, amputation, end-stage kidney disease, blindness, and death.
Diabetes is Expensive

Diagnosed diabetes costs ~$9.7 billion in MI each year

- Total direct medical expenses were ~$7 billion in 2017
- Another $2.7 billion was spent on indirect costs from lost productivity due to diabetes

People with diabetes have medical expenses ~2.3 times higher than those who don’t have diabetes
Current State of Diabetes Management

8.4
Average A1C% level of type 1 patients

69%
Insulin using patients above ADA A1C target of 7%

70%
Patients not taking their insulin as prescribed

The barriers to good glycemic control are wide-ranging and far-reaching, contributing not only to long-term complications but also hindering a patient’s day-to-day quality of life.
T2DM is an endocrine and metabolic disorder characterized by:

- Insulin secretion deficits
- High blood glucose levels
- Glucagon secretion
- Insulin resistance
- If left untreated, can cause target organ damage
- Microvascular complications
- Macrovascular complications
PCPs Role

- Initiate preventive measures
- Develop therapeutic management plans
- Monitor patients BG levels effectively through follow-up visits and referrals
- Teach patient to provide self-care
- Manage comorbid conditions: BP control, Lipid control, Antiplatelet agents
- Follow-up and referrals
### Office Visits

1. Assess A1C levels
2. Monitor BG logs
3. Evaluate medication dosages and adherence
4. Screen for weight gain or loss
5. Measure BP and lipid levels
6. Assess foot care
7. Assess nutrition and exercise
8. Annual urinalysis for microalbuminuria, health exam, dental care, glaucoma screening
Guidelines for Diabetes Management
General Traditional Classifications

Type 1 diabetes (T1DM) accounts for 5-10% of diabetes, occurs in youth, is defined by the body having beta cell destruction (therefore insulin deficiency).

Type 2 diabetes (T2DM) accounts for 90-95% of diabetes, occurs in adults, is hallmarked by the body systemically having insulin resistance (therefore at first insulin excess and beta cell function).
Classifying Diabetes

Four overall general categories:

- Type 1 Diabetes (T1DM)
- Type 2 Diabetes (T2DM)
- Gestational Diabetes
- Types of diabetes due to “other specific causes”

- All of these categories are further divided, heterogeneous in clinical presentation have variable progression, and may not be mutually exclusive
- In general the true classification becomes more apparent with time
Classifying Diabetes

Once persistent hyperglycemia occurs, in all forms of diabetes (though the rates of progression vary), these people are at risk for developing the same chronic complications.

The intervention of therapy is dependent on the classification of the type of diabetes and the risk of complications.
Classifying Diabetes

The observation of risk factors, symptoms, elevated blood glucoses, and HbA1c are important even prior to knowing the classification of diabetes.

With these observations, it is also feasible to change the risk of future complications and even stop the diagnosis of diabetes.

With these observations, it is feasible to intervene and therefore avert the onset of diabetes induced ketoacidosis.
<table>
<thead>
<tr>
<th><strong>Type 2 Diabetes</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously known as “noninsulin-dependent diabetes” or “adult-onset diabetes”</td>
</tr>
<tr>
<td>Accounts for 90-95% of diabetes</td>
</tr>
<tr>
<td>Due to the loss of beta cell secretion, frequently on the background of insulin resistance</td>
</tr>
<tr>
<td>Adults may present with abnormal labs, weight loss, polyuria, polydipsia, and even ketosis (particularly in ethnic minorities in the US)</td>
</tr>
</tbody>
</table>
Type 2 Diabetes

- Subset called ketosis prone or “Flatbush” diabetes
- Occurs more frequently in individuals with African ancestry
- With lack of medicinal intervention can “slip” into DKA
- Amazingly, sometimes lifestyle changes can even achieve euglycemia without medical intervention
- Sometimes could be referred to as Type 1b
Types Due to “other causes”

<table>
<thead>
<tr>
<th>Medication induced:</th>
<th>Monogenic Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Glucocorticoids, thiazide diuretics, and atypical antipsychotics are known to increase the risk of diabetes</td>
<td>• Certain genetic changes in individuals can create beta cell dysfunction</td>
</tr>
<tr>
<td>• Steroid (glucocorticoid) induced diabetes is fairly common in patients with rheumatologic disorders, inflammatory bowel diseases, COPD, asthma, and transplant patients</td>
<td>• Later discoveries of genetic etiologies have led to groups of people with diagnosed monogenic diabetes syndromes</td>
</tr>
</tbody>
</table>
Types Due to “other causes”

• Monogenic defects that cause beta-cell dysfunction are known as neonatal diabetes and maturity-onset diabetes of the young (MODY)

• This classification of diabetes represents a small (<5%) portion of patients with diabetes

• “Neonatal” or “Congenital” diabetes:
  • All children diagnosed with diabetes in the first 6 months of life should have immediate genetic testing for neonatal diabetes
  • 80-85% of cases can be found to have an underlying monogenic cause
  • Certain genetic versions can be treated properly and safely with oral sulfonylurea, and therefore forego insulin injection therapy

• Autoimmune type 1 diabetes rarely occurs before 6 months of age
Types Due to “other causes”
Maturity-onset diabetes of the young (MODY)

Consider in individuals who have atypical diabetes and multiple family members with diabetes not characteristic of Type 1 or Type 2 diabetes.

The presence of autoantibodies for Type 1 diabetes precludes further testing for monogenic diabetes.

Usually respond well to low doses of sulfonylureas, which are considered first line therapy.
Nonpharmacologic Management

- **Lifestyle Modifications**
  - Regular physical activity and exercise
  - Behavioral support: smoking cessation, self-care management, alcohol moderation, substance use disorder counseling, stress reduction
- **Healthy nutrition**
  - Weight self-management
  - Medical management
  - Surgical management
  - Structured diet programs
Nonpharmacologic Management cont.

- Diabetes education
  - Glycemic control
  - Technology tools can use
- Self-glucose management
  - Self-monitoring blood glucose (SMBG)
  - Continuous glucose monitoring (CGM)
- Behavioral support
Pharmacologic Management
Antihyperglycemic agents

• Biguanides
• GLP1 agonists
• SG LT2s
• DPP-4 Inhibitors
• Insulin therapy
  • Pens and vials
  • V-Go
  • Insulin pumps
GLP-1 Receptor Agonists

- Incretin mimetics enhance insulin secretion, inhibit glucagon secretion, induce satiety, delay gastric emptying
- Exanatide (Byetta), Exanatide ER (Bydureon), liraglutide (Victoza), Dulaglutide (Trulicity), lizisenatide (Adlyxin), Sema glutide (Ozempic)
SG LT2 Inhibitors

- Selective sodium-glucose cotransporter inhibitors
- Empagliflozin (Jardiance), canagliflozin (Invokana), dapagliflozin (Farxiga), ertugliflozin (Steglatro)
- Renal Benefits
Urinary glucose excretion via SGLT2 inhibition

Filtered glucose load > 180 g/day

SGLT2 inhibitor

SGLT1

SGLT2 inhibitors reduce glucose reabsorption in the proximal tubule, leading to urinary glucose excretion and osmotic diuresis.

DPP-IV Inhibitors (Gliptins)

- Reduce breakdown of GLP-1 (which increases insulin secretion and promotes satiety)
- Alogliptin (Nesina), Sitagliptin (Januvia), saxagliptin (Onglyza), linagliptin (Tradjenta)
- Effectively reduces HgbA1c in CKD stages 3 and 4
- Appears safe
- May have some renoprotective effects; reduction in albuminuria seen in several studies
DPP4 inhibitors: Mechanism of action

Food Intake → Intestine → Pancreas

β-cells
Increase glucose utilisation by muscle and adipose tissue

α-cells
Glucose-dependent glucagon suppression
Decreases hepatic glucose release improving overall glucose control

Active GLP1 (7-36) → DPP4 → Inactive GLP1 (9-36) amidate

DPP4 inhibitors
2 amino acids cleaved from amino terminus

Three Levels of Prevention

- Primary Prevention
  - Risk factors
  - Nutrition Interventions
  - Environmental modifications
  - Behavior changes
- Secondary Prevention
  - Early diagnosis of T2DM
Three Levels of Prevention cont.

• Tertiary Prevention
  • How to preclude physiologic and psychological impairments
  • Long-term treatment adherence
  • Disease complication prevention
  • Minimizing adverse reactions associated with medications
  • Promoting healthy lifestyles and practices
  • Follow-up care with other multidisciplinary measures
Diabetes is a CVD Equivalent

Diabetes Mellitus: Risk of Myocardial Infarction

East-West Study

Events* / 100 person-years

<table>
<thead>
<tr>
<th>Prior CHD</th>
<th>DM</th>
<th>No DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>19.0</td>
<td>3.5</td>
<td></td>
</tr>
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</table>

Source: Haffner SM et al. NEJM 1998;339:229–234
Preventing Diabetic Complications
Two-Track Approach to Reduce Risk

**Track 1**
Lower glucose to prevent microvascular complications and progression to diabetes
- **Lifestyle** intervention
- **Pharmacotherapy** in high risk patients

**Track 2**
Address cardiovascular disease risk factors
- **Lifestyle** intervention
- **Blood pressure goals**: <130/80 mm Hg
- **LDL goal**: <100 mg/dL
Reduction in Life Expectancy for a 50 yo with Type 2 DM (years)

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
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<tbody>
<tr>
<td>T2DM</td>
<td>-7.2</td>
<td>-7.8</td>
</tr>
<tr>
<td>T2DM + MI</td>
<td>-14.8</td>
<td>-18.1</td>
</tr>
<tr>
<td>T2DM + Stroke</td>
<td>-14.5</td>
<td>-15.5</td>
</tr>
<tr>
<td>T2DM + MI + Stroke</td>
<td>-19.8</td>
<td>-19.1</td>
</tr>
</tbody>
</table>

JAMA 2015; 314(1): 52-60
Treating CV Risk Factors
Effect of Improving Glycemic Control

**DCCT**
T1DM, 5-6 years duration (N=1441)

42% risk reduction
**P=0.02**

**UKPDS**
T2DM, newly diagnosed (N=4209)

15% risk reduction
**P=0.01**

CV, cardiovascular; DCCT, Diabetes Control and Complications Trial; MI, myocardial infarction; UKPDS, United Kingdom Prospective Diabetes Study.
## Treating the ABCs Reduces Diabetic Complications

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Complication</th>
<th>Reduction of Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood glucose control</strong></td>
<td>• Myocardial infarction</td>
<td>↓ 15%&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Blood pressure control</strong></td>
<td>• Cardiovascular disease</td>
<td>↓ 51%&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• Heart failure</td>
<td>↓ 55%&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• Stroke</td>
<td>↓ 44%&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• Diabetes-related deaths</td>
<td>↓ 32%&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Lipid control</strong></td>
<td>• Coronary heart disease mortality</td>
<td>↓ 35%&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• Major coronary heart disease event</td>
<td>↓ 55%&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• Any atherosclerotic event</td>
<td>↓ 37%&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• Cerebrovascular disease event</td>
<td>↓ 53%&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

CV Risk Reduction
How Well Are We Doing?


Casagrande SS, Frackin JE, Saydah SH, Rust KF, Cowie CC. Diabetes Care 2013;36:2271-2279
Cardiovascular Outcomes Trials (CVOTs): A Brief History

2008 FDA guidance mandating assessment of CV safety of all antihyperglycemic agents in RCTs
  – Designed as noninferiority studies to demonstrate study drug was not associated with more MACE than placebo
    • Some study designs tested for superiority if noninferiority criteria were met
  – Primary endpoint: composite of cardiovascular death, nonfatal MI, and nonfatal stroke
    • Some primary endpoints included additional components

MACE = major adverse cardiovascular events; RCTs, randomized controlled trials.
# Summary of CV outcomes trials with DPP4 inhibitors

<table>
<thead>
<tr>
<th>Intervention</th>
<th>SAVOR-TIMI 53 (^1)</th>
<th>EXAMINE (^2)</th>
<th>TECOS (^3)</th>
<th>CAROLINA (^4)</th>
<th>CARMELINA (^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main inclusion criteria</strong></td>
<td>Saxagliptin/placebo</td>
<td>Alogliptin/placebo</td>
<td>Sitagliptin/placebo</td>
<td>Linagliptin/glimepride</td>
<td>Linagliptin/placebo</td>
</tr>
<tr>
<td><strong>No. of patients</strong></td>
<td>16,492</td>
<td>5380</td>
<td>14,671</td>
<td>6041</td>
<td>8300</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td>3P-MACE</td>
<td>3P-MACE</td>
<td>4P-MACE</td>
<td>4P-MACE</td>
<td>4P-MACE</td>
</tr>
<tr>
<td><strong>Key secondary outcome</strong></td>
<td>Expanded MACE</td>
<td>4P-MACE</td>
<td>3P-MACE</td>
<td>3P-MACE</td>
<td>3P-MACE; renal composite</td>
</tr>
<tr>
<td><strong>Target no. of events</strong></td>
<td>1040 (^6)</td>
<td>650</td>
<td>1300</td>
<td>631</td>
<td>625 (^7)</td>
</tr>
<tr>
<td><strong>Median follow-up (y)</strong></td>
<td>2.1</td>
<td>1.5</td>
<td>3.0</td>
<td>6–7 (^*)</td>
<td>4 (^*)</td>
</tr>
<tr>
<td><strong>CVOT Result</strong></td>
<td>NEUTRAL</td>
<td>NEUTRAL</td>
<td>NEUTRAL</td>
<td>2018 (^8)</td>
<td>NEUTRAL</td>
</tr>
</tbody>
</table>

\(^{*}\) Ongoing.

GLP1 has various potential effects on the CV system:
Data derived from non-clinical and mechanistic proof-of-concept studies

**Incretin hormone**

**Pancreas**
- ↑ Insulin secretion
- ↓ Glucagon secretion
- ↑ Insulin biosynthesis
- ↑ β-cell proliferation
- ↓ β-cell apoptosis

**Brain**
- ↓ Appetite
- ↑ Neuroprotection

**Liver**
- ↓ Glucose output

**Muscle and adipose tissue**
- ↑ Insulin sensitivity (direct or indirect?)

**Heart**
- ↑ Endothelial function
- ↑ Nitric oxide production
- ↓ Myocardial contractility (data conflict)
- ↑ Systolic function in myocardial infarction
- ↑ Systolic function in cardiomyopathy
- ↓ Infarct size
- ↑ Ischaemic pre-conditioning
- ↑ Post-ischaemic recovery
- ↑ Myocardial glucose uptake

Clinical trial data show that GLP1 receptor agonists are associated with small increases in heart rate and modest reductions in body weight and blood pressure.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Main inclusion criteria</th>
<th>No. of patients</th>
<th>Primary outcome</th>
<th>Key 2nd outcome</th>
<th>Target no. of events</th>
<th>Estimated follow-up</th>
<th>Estimated completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIXA(^1,2)</td>
<td>Lixisenatide/placebo, History of ACS</td>
<td>6068</td>
<td>4P-MACE</td>
<td>Expanded MACE</td>
<td>844</td>
<td>2.1 years median</td>
<td>Completed</td>
</tr>
<tr>
<td>LEADER(^3)</td>
<td>Liraglutide/placebo, Vascular disease, or risk factors, or CRF, or CHF</td>
<td>9340</td>
<td>3P-MACE</td>
<td>Expanded MACE</td>
<td>&gt; 611</td>
<td>Up to ~5 years</td>
<td>Completed</td>
</tr>
<tr>
<td>SUSTAIN-6(^4)</td>
<td>Semaglutide/placebo, Evidence of CV disease</td>
<td>3297</td>
<td>3P-MACE</td>
<td>Expanded MACE</td>
<td>Not specified</td>
<td>Up to ~3 years</td>
<td>Completed</td>
</tr>
<tr>
<td>EXCEL(^5)</td>
<td>Exenatide ER(^7)/placebo, No CV criteria specified</td>
<td>14,000</td>
<td>3P-MACE</td>
<td>All-cause mortality; HHF</td>
<td>Not specified</td>
<td>Up to ~7.5 years</td>
<td>Completed</td>
</tr>
<tr>
<td>REWIND(^6)</td>
<td>Dulaglutide/placebo, Pre-existing vascular disease or ≥2 CV risk factors</td>
<td>9622</td>
<td>3P-MACE</td>
<td>Microvascular composite</td>
<td>Not specified</td>
<td>Up to ~6.5 years</td>
<td>Completed</td>
</tr>
</tbody>
</table>

*Once weekly.
Clinical Outcomes with Liraglutide

**LEADER (N=9340)**

Median follow-up: 3.5 years

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint*</td>
<td>0.87 (0.78-0.97)</td>
<td>0.01</td>
</tr>
<tr>
<td>Expanded composite endpoint†</td>
<td>0.88 (0.81-0.96)</td>
<td>0.005</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>0.85 (0.74-0.97)</td>
<td>0.02</td>
</tr>
<tr>
<td>CV death</td>
<td>0.78 (0.66-0.93)</td>
<td>0.007</td>
</tr>
<tr>
<td>Fatal or nonfatal MI</td>
<td>0.86 (0.73-1.00)</td>
<td>0.046</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>0.78 (0.67-0.92)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*CV death, nonfatal MI (including silent MI), or nonfatal stroke.
†CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, and hospitalization for unstable angina or HF.

CI, confidence interval; CV, cardiovascular; MI, myocardial infarction.

## Clinical Outcomes with Semaglutide

**SUSTAIN 6 Results**  
(N=3297)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint*</td>
<td>0.74 (0.58-0.95)</td>
<td>0.02</td>
</tr>
<tr>
<td>Expanded composite endpoint†</td>
<td>0.88 (0.81-0.96)</td>
<td>0.002</td>
</tr>
<tr>
<td>All-cause death, nonfatal MI, nonfatal stroke</td>
<td>0.77 (0.61-0.97)</td>
<td>0.03</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>1.05 (0.74-1.50)</td>
<td>0.79</td>
</tr>
<tr>
<td>CV death</td>
<td>0.98 (0.65-1.48)</td>
<td>0.92</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>0.74 (0.51-1.08)</td>
<td>0.12</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>0.61 (0.38-0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Revascularization</td>
<td>0.65 (0.50-0.86)</td>
<td>0.003</td>
</tr>
<tr>
<td>Retinopathy complications</td>
<td>1.76 (1.11-2.78)</td>
<td>0.02</td>
</tr>
<tr>
<td>New or worsening nephropathy</td>
<td>0.64 (0.46-0.88)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*CV death, nonfatal MI (including silent MI), or nonfatal stroke; †CV death, nonfatal MI, nonfatal stroke, coronary or peripheral revascularization, and hospitalization for unstable angina or HF.

CI, confidence interval; CV, cardiovascular; HF, heart failure; MI, myocardial infarction.

Clinical Outcomes with Exenatide

EXSCEL (N=14,752)

Median follow-up: 3.2 years

<table>
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<tr>
<th>Event</th>
<th>Hazard ratio (95% CI)</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint*</td>
<td>0.91 (0.83-1.00)</td>
<td>0.06</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>0.86 (0.77-0.97)</td>
<td>NS</td>
</tr>
<tr>
<td>CV death</td>
<td>0.88 (0.76-1.02)</td>
<td></td>
</tr>
<tr>
<td>Fatal or nonfatal MI</td>
<td>0.97 (0.85-1.10)</td>
<td></td>
</tr>
<tr>
<td>Fatal MI</td>
<td>1.29 (0.63-2.66)</td>
<td></td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>0.85 (0.70-1.03)</td>
<td></td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>0.71 (0.39-1.30)</td>
<td></td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>0.94 (0.78-1.13)</td>
<td></td>
</tr>
<tr>
<td>Hospitalization for ACS</td>
<td>1.05 (0.94-1.18)</td>
<td></td>
</tr>
</tbody>
</table>

*CV death, nonfatal MI, or nonfatal stroke. †For superiority.

ACS, acute coronary syndrome; CI, confidence interval; CV, cardiovascular; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; HF, heart failure; MI, myocardial infarction; NS, not statistically significant based on hierarchical testing plan.

Clinical Outcomes with Dulaglutide

REWIND
(N=9,901)
Median follow-up: 5.4 years

November 5, 2018

Dulaglutide significantly reduced major adverse cardiovascular events (MACE),
- cardiovascular (CV) death
- non-fatal myocardial infarction
- non-fatal stroke

Majority of participants did not have established CV disease (69%).

Baseline HbA1c was 7.3%

Full Data to be reported at 2019 ADA Scientific Sessions
### Summary of CV outcomes trials with GLP1 receptor agonists

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<tr>
<th>Intervention</th>
<th>Main inclusion criteria</th>
<th>No. of patients</th>
<th>Primary outcome</th>
<th>Key 2° outcome</th>
<th>Target no. of events</th>
<th>Estimated follow-up</th>
<th>CVOT RESULT</th>
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<td>Expanded MACE</td>
<td>Not specified</td>
<td>Up to ~3 years</td>
<td>POSITIVE</td>
</tr>
<tr>
<td>EXCEL&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Exenatide ER&lt;sup&gt;5&lt;/sup&gt;/placebo, No CV criteria specified</td>
<td>14,000</td>
<td>3P-MACE</td>
<td>All-cause mortality; HHF</td>
<td>Not specified</td>
<td>Up to ~7.5 years</td>
<td>NEUTRAL</td>
</tr>
<tr>
<td>REWIND&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Dulaglutide/placebo, Pre-existing vascular disease or ≥2 CV risk factors</td>
<td>9622</td>
<td>3P-MACE</td>
<td>Microvascular composite</td>
<td>Not specified</td>
<td>Up to ~6.5 years</td>
<td>POSITIVE</td>
</tr>
</tbody>
</table>

*Once weekly.
## Pharmacological properties of available SGLT2 inhibitors

<table>
<thead>
<tr>
<th>Therapeutic dose (mg/day)</th>
<th>Empagliflozin</th>
<th>Dapagliflozin</th>
<th>Canagliflozin</th>
<th>Ertugliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>10–25</td>
<td>10</td>
<td>100–300</td>
<td>5-15</td>
</tr>
<tr>
<td>Administration</td>
<td>QD</td>
<td>QD</td>
<td>QD</td>
<td>QD</td>
</tr>
<tr>
<td>With or without food</td>
<td>With or without food</td>
<td>With or without food</td>
<td>With or without food</td>
<td></td>
</tr>
</tbody>
</table>

- **Peak plasma concentration (hours post-dose)**
  - Empagliflozin: Within 2 hours
  - Dapagliflozin: 1–2 hours
  - Canagliflozin: 0.5–1.5 hours
  - Ertugliflozin: ~90%

- **Absorption (mean oral bioavailability)**
  - Empagliflozin: ≥ 60%
  - Dapagliflozin: ~ 78%
  - Canagliflozin: ~ 65%
  - Ertugliflozin: ~90%

- **Metabolism**
  - Primarily glucuronidation - no active metabolite

- **Elimination (half-life, hours)**
  - Empagliflozin: 43.57 [12.4]
  - Dapagliflozin: 22.78 [12.9]
  - Canagliflozin: 67.33 [13.1]*
  - Ertugliflozin: 61.39 [13.1]*

- **Selectivity over SGLT1**
  - Empagliflozin: 1:5000
  - Dapagliflozin: > 1:1400
  - Canagliflozin: > 1:160¹
  - Ertugliflozin: > 1:2000

- **Glucose excretion with higher dose (g/day)**
  - Empagliflozin: 78
  - Dapagliflozin: ~ 70
  - Canagliflozin: 119
  - Ertugliflozin: ~50 grams

*For the 300 mg dose.
SGLT2 inhibitors modulate a range of factors related to CV risk
Based on clinical and mechanistic studies

- Blood pressure
- Arterial stiffness
- Albuminuria
- SNS activity (?)
- Glucose
- Insulin
- Uric Acid
- Weight
- Visceral adiposity
- Oxidative stress
- LDL-C
- HDL-C
- Triglycerides

### Clinical Outcomes with Empagliflozin

**EMPA-REG OUTCOME Pooled Analysis**
(N=7020)

Median follow-up: 3.1 years

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

*CV death, nonfatal MI (excluding silent MI), or nonfatal stroke; †CV death, nonfatal MI (excluding silent MI), nonfatal stroke, and hospitalization for unstable angina.

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

# Microvascular and Renal Outcomes with Empagliflozin

**EMPA-REG RENAL**  
(N=7020)

**Median follow-up: 3.1 years**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite microvascular endpoint*</td>
<td>0.62 (0.54-0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incident or worsening nephropathy or CV death</td>
<td>0.61 (0.55-0.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incident or worsening nephropathy</td>
<td>0.61 (0.53-0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progression to microalbuminuria</td>
<td>0.62 (0.54-0.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Doubling of Scr plus eGFR ≤45 mL/min/1.73 m²</td>
<td>0.56 (0.39-0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Initiation of renal replacement therapy</td>
<td>0.45 (0.21-0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>Severe renal outcomes†</td>
<td>0.54 (0.40-0.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incident albuminuria in patients with normal albumin at baseline</td>
<td>0.95 (0.87-1.04)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

*In patients with normal albuminuria at baseline.

CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate in mL/min/1.73 m²; HR, hazard ratio; Scr, serum creatinine.

Clinical Outcomes with Canagliflozin

CANVAS Program
(N=10,142)

Median follow-up: 2.4 years

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint*</td>
<td>0.86 (0.75-0.97)</td>
<td>0.021</td>
</tr>
<tr>
<td>CV death</td>
<td>0.87 (0.72-1.06)</td>
<td></td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>0.85 (0.69-1.05)</td>
<td></td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>0.90 (0.71-1.15)</td>
<td></td>
</tr>
<tr>
<td>Fatal or nonfatal MI</td>
<td>0.89 (0.73-1.09)</td>
<td></td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>0.87 (0.69-1.09)</td>
<td></td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>0.67 (0.52-0.87)</td>
<td></td>
</tr>
<tr>
<td>CV death or HF hospitalization</td>
<td>0.78 (0.67-0.91)</td>
<td></td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.87 (0.74-1.01)</td>
<td></td>
</tr>
<tr>
<td>Progression of albuminuria</td>
<td>0.73 (0.67-0.79)</td>
<td></td>
</tr>
<tr>
<td>40% reduction in eGFR, renal replacement therapy, or renal death</td>
<td>0.60 (0.47-0.77)</td>
<td></td>
</tr>
</tbody>
</table>

*CV death, nonfatal MI, or nonfatal stroke. †Superiority.
CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.
# Summary of CV outcome trials with SGLT2 inhibitors

<table>
<thead>
<tr>
<th>Interventions</th>
<th>EMPA-REG OUTCOME&lt;sup&gt;1&lt;/sup&gt;</th>
<th>CANVAS&lt;sup&gt;2&lt;/sup&gt;</th>
<th>CANVAS-R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>CREDENCE&lt;sup&gt;4&lt;/sup&gt;</th>
<th>DECLARE-TIMI 58&lt;sup&gt;5&lt;/sup&gt;</th>
<th>Ertugliflozin CVOT&lt;sup&gt;6&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main inclusion criteria</td>
<td>Empagliflozin/placebo</td>
<td>Canagliflozin/placebo</td>
<td>Canagliflozin/placebo</td>
<td>Canagliflozin/placebo</td>
<td>Stage 2 or 3 CKD + macroalbuminuria</td>
<td>High risk for CV events</td>
</tr>
<tr>
<td>No. of patients</td>
<td>7034</td>
<td>4339</td>
<td>5700</td>
<td>3627</td>
<td>17,160</td>
<td>3900</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>3P-MACE</td>
<td>3P-MACE</td>
<td>Progression of albuminuria</td>
<td>ESKD, S-creatinine doubling, renal/CV death</td>
<td>3P-MACE</td>
<td>3P-MACE</td>
</tr>
<tr>
<td>Key secondary outcome</td>
<td>4P-MACE</td>
<td>Fasting insulin secretion, progression of albuminuria</td>
<td>Regression of albuminuria, change in eGFR</td>
<td>4P-MACE + HHF</td>
<td>4P-MACE + HHF + revascularisation</td>
<td>4P-MACE</td>
</tr>
<tr>
<td>Target no. of events</td>
<td>691</td>
<td>≥ 420</td>
<td>TBD</td>
<td>TBD</td>
<td>1390</td>
<td>TBD</td>
</tr>
<tr>
<td>Estimated median FU</td>
<td>~3 years</td>
<td>6–7 years</td>
<td>3 years</td>
<td>~4 years</td>
<td>4–5 years</td>
<td>5–7 years</td>
</tr>
</tbody>
</table>

CVOT Results: POSITIVE/POSITIVE/POSITIVE 2019 -MACE / + HF 2021

Limitations of self-monitoring blood glucose (SMBG) and HbA1c

**SMBG**
- Provides glucose information for only points in time, however:
  - Hypoglycemia and hyperglycemia are often missed
  - Overnight data is impractical to obtain
  - Logbooks can be difficult to interpret

**HbA1c**
- Standard of Care, however:
  - Impact of hypoglycemia and hyperglycemia are unknown
  - Unknown glucose variability
Potential Clinician Recommendations in Response to Frequent or Severe Hypoglycemia

- Loosen control - establish higher glucose targets
- Increase SMBG frequency
- Change insulin delivery to a pump
- Change SMBG to CGM
Glycemic Variability

- Pathophysiologic data indicates increased oxidative stress occurs with fluctuating levels.
- Epidemiologic studies suggest correlation between elevated post-meal glucose levels and micro- and macrovascular outcomes.
- The effect of fluctuations of glucose levels, not only the management of chronic hyperglycemia, is hypothesized as a variable though more data is needed to determine it as an independent variable.
- However, the goal is “Time In Range”
Why Is It So Important to Avoid Hypoglycemia?

Hypoglycemia is Always Clinically Significant\(^1,2\)  
Severe Hypoglycemia Is Costly\(^6\)

**Severe**\(^1,2\)
- Requires assistance from others to treat
- May result in death

**Nonsevere**\(^3,5\)
- May require hours of recovery time
- May impair productivity, attendance at work
- Reduces quality of life

**Nocturnal**\(^3\)
- Interferes with sleep
- May not be detected early enough to self-treat

Hypoglycemia is a common reason for insulin discontinuation\(^7,8\)

---

Finger stick Testing Does Not Show the Whole Picture

Fingerstick 4.2 hours after passing 210 mg/dL

Above 210 mg/dL for 4.8 hours

Above 140 mg/dL for 13.5 hours

Glucose (mg/dL)

Target Range

ONE IS ASKING A QUESTION: THE OTHER IS ANSWERING

- **METER**: Still leaves the question
- **AM I 80 mg/dL going up or down?**
- **How fast is my glucose changing?**

- **CGM**: Answers the question
- I am 80 mg/dL going down.
- My glucose is going down fast at a rate of > 3 mg/dL/min

CGMs can provide the answers and a more complete picture to allow patients to make safe, well-informed treatment decisions.
Continuous Glucose Monitoring (CGM)

◆ ‘Traditional’ CGM systems provide real-time or continuous (streaming) blood glucose data every 5 minutes with real-time alerts for pre-set high and low blood glucose thresholds.

◆ ‘Flash’ CGM systems provide data every 15 minutes when a reader or scanner device is held over the sensor, but does not provide real-time alerts or streaming data to a receiver device.
Glucose oxidase reaction
Dexcom G6 Sensor and Transmitter

- Real-time, *Integrated* Continuous Glucose Monitor
- FDA approved for **non-adjunctive use in ages 2 and older**
- Sensor wear time: up to 10 days
- 2-hour start-up time
- No calibrations required
- Fingersticks not required for treatment decisions
- Glucose readings every 5 minutes
- Remote monitoring
Abbott FreeStyle Libre Sensor and Reader

- Flash Glucose Monitoring
- FDA approved for non-adjunctive use in ages 18 and older
- Sensor wear time: up to 14 days
- 1-hour start-up time
- No calibrations required, but patients are encouraged to check BG:
  - When readings do not match sympoms
  - During first 12 hours of wear
  - To confirm hypoglycemia
  - When glucose is rapidly rising or falling
- Glucose readings every 15 minutes
- Data uploaded from reader using FreeStyle LibreView software
Medtronic Guardian 3 Sensor and Transmitter

- Real-time Continuous Glucose Monitor
- FDA approved for **adjunctive use in ages 14 and older**
- Sensor wear time: up to 7 days
- 2-hour start-up time
- Calibrations every 12 hours
- Glucose readings every 5 minutes
Eversense Implantable Sensor and Transmitter

- Real-time Continuous Glucose Monitor
- FDA approved for **adjunctive use in ages 18 and older**
- Implanted sensor use time: up to 90 days
- 24-hour start-up time
- Calibrations every 12 hours then four calibrations are required
- Glucose readings every 5 minutes
- Sensor powered wirelessly by rechargeable transmitter
Patient Selection

- Adults and children ≥2 years of age with T1D or T2D on either an MDI or a CSII regimen
- Centers for Medicare & Medicaid Services covers CGM for individuals with T1D or T2D on CSII therapy or ≥3 daily insulin injections
- Pregnant women with diabetes (not approved)
- Patients with hypoglycemia unawareness
- Patients with significant fear of hypoglycemia
- To get and keep patients BG “Time in Range”
- Individuals with vision loss or impaired dexterity should not be excluded
Data Interpretation Pointers

- Previous 14 days correlates well with past 3 months
- Must be worn ≥70% of the time or 10 of the past 14 days
- Average glucose (correlates closely to A1C)
- Variability (SD/coefficient of variation)
- Time in range (70–180 mg/dL)
- Time in hypoglycemia (<70 mg/dL and <54 mg/dL)
CGM Patient Education

- Basic Education regarding device, skin care, insertion, accuracy
- **Non-adjunctive use**, NO FINGER STICKS NEEDED
- How to use data, sharing data
- Using data daily and Big Picture
- Utilizing Arrows
- Realistic expectations of CGM capabilities
- Consistent wear
- Ongoing education - the CGM learning curve
- Getting patients involved in data analysis and successes
How do CGM-based decisions enable CGM users to improve glucose control?

**Lower A1C**
- Larger insulin dose for rising glucose
- Respond to high glucose alerts at night, decreasing nocturnal hyperglycemia
- More frequent correction boluses/ injections
- Lower glucose targets
- Increase timing between insulin dose and meal for rising glucose

**Reduce Hypoglycemia**
- Reduce or eliminate insulin doses for falling glucose
- Respond to low glucose alerts
- Prophylactically treating with carbohydrates to prevent lows when glucose is falling
- Decrease timing between insulin dose and meal for falling glucose

### Directional Arrows

<table>
<thead>
<tr>
<th>Dexcom G5/G6</th>
<th>Guardian Connect</th>
<th>FreeStyle Libre</th>
<th>Eversense</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arrow</strong></td>
<td><strong>Meaning</strong></td>
<td><strong>Arrow</strong></td>
<td><strong>Meaning</strong></td>
</tr>
<tr>
<td>↑↑</td>
<td>Glucose rapidly rising increasing &gt;3 mg/dL/min</td>
<td>↑↑</td>
<td>Glucose rapidly rising increasing &gt;3 mg/dL/min</td>
</tr>
<tr>
<td>↑</td>
<td>Glucose rising increasing 2-5 mg/dL/min</td>
<td>↑↑</td>
<td>Glucose is rising 2-3 mg/dL/min</td>
</tr>
<tr>
<td>↑↑</td>
<td>Glucose slowly rising increasing 1-2 mg/dL/min</td>
<td>↑</td>
<td>Glucose slowly rising 1-2 mg/dL/min</td>
</tr>
<tr>
<td>↑</td>
<td>Glucose steady increasing/decreasing &lt;1 mg/dL/min</td>
<td></td>
<td>Glucose steady increasing/decreasing &lt;1 mg/dL/min</td>
</tr>
<tr>
<td>↓</td>
<td>Glucose slowly falling 1-2 mg/dL/min</td>
<td>↓</td>
<td>Glucose slowly falling 1-2 mg/dL/min</td>
</tr>
<tr>
<td>↓</td>
<td>Glucose falling 2-3 mg/dL/min</td>
<td>↓</td>
<td>Glucose is falling 2-3 mg/dL/min</td>
</tr>
<tr>
<td>↓</td>
<td>Glucose rapidly falling decreasing &gt;3 mg/dL/min</td>
<td></td>
<td>Glucose rapidly falling &gt;2 mg/dL/min</td>
</tr>
</tbody>
</table>
Directional Arrows
CGM Diabetes Management Guidelines

General guidelines
- Wear the CGM as much as possible
- Look at your receiver frequently
- Alerts and alarms should be your friend, not your enemy
- Share your CGM results
- Reflect on your past decisions
- CGM is not perfect, nor is your meter (calibration)

Personalized guidelines
- Know your glucose targets
- Have a plan for preventing or responding to low glucose
- Adjust meal-time insulin dose and timing based on the direction and rate of glucose change
- Respond to high glucose levels between meals but avoid "stacking" insulin
Company Websites

- **Dexcom**: [https://www.dexcom.com/dexcom-care-tutorials-and-online-education](https://www.dexcom.com/dexcom-care-tutorials-and-online-education)
- **Abbott FreeStyle Libre**: [https://www.myfreestyle.com/provider/freestyle-libre-resources](https://www.myfreestyle.com/provider/freestyle-libre-resources)
- **Medtronic**: [https://www.medtronicdiabetes.com/services/training-education](https://www.medtronicdiabetes.com/services/training-education)
- **Senseonics Eversense**: [https://www.eversensediabetes.com/patient-education/](https://www.eversensediabetes.com/patient-education/)
Real-Time CGM is the NEW Standard of Care for Patients on Intensive Insulin

- Recognized as a standard of care in diabetes management by the American Diabetes Association (ADA), American Association of Clinical Endocrinologists (AACE) and the Endocrine Society. 1,2,3

- Continuous glucose monitoring (CGM) use has proven to both reduce A1C and time spent in hypoglycemia regardless of delivery method. 4,5

- Regular CGM use is also associated with an increase of time spent in range,4,6 a reduction of severe hypoglycemic incidents,7,8 and associated with many behavioral changes that promote significant positive change in diabetes self-management.9