Mastering the outpatient Type 2 Management

Jorge De Jesús MD
Objectives:

After this presentation you will be able to recognize:

- Diabetes Mellitus is a progressive disease
- Prevention is possible for selected high risk individuals

- Outline the clinical considerations in the selection of pharmacotherapy for type 2 diabetes, including degree of A1C lowering achieved, patient-specific concerns, adverse drug reactions, and contraindications
- Discuss the role and timing of combination therapy in achieving A1C goals
- Explain the implications of recent, large randomized clinical trials on clinical decision-making
- Modifications in 2019 ADA guidelines based on recent RCT trials
T2DM is a progressive disease: Do microvascular and macrovascular complications begin at different times?

Adapted from DeFronzo RA. Med Clin N Am 2004;88:787-835.
LIFESTYLE THERAPY
RISK STRATIFICATION FOR DIABETES COMPLICATIONS

INTENSITY STRATIFIED BY BURDEN OF OBESITY AND RELATED COMPLICATIONS

**Nutrition**
- Maintain optimal weight
- Calorie restriction (if BMI is increased)
- Plant-based diet; high polyunsaturated and monounsaturated fatty acids
- Avoid trans fatty acids; limit saturated fatty acids
- Structured counseling; Meal replacement

**Physical Activity**
- 150 min/week moderate exertion (e.g., walking, stair climbing)
- Strength training
- Increase as tolerated
- Structured program
- Wearable technologies
- Medical evaluation/clearance
- Medical supervision

**Sleep**
- About 7 hours per night
- Basic sleep hygiene
- Screen OSA
- Home sleep study
- Referral to sleep lab

**Behavioral Support**
- Community engagement
- Alcohol moderation
- Discuss mood with HCP
- Formal behavioral therapy

**Smoking Cessation**
- No tobacco products
- Nicotine replacement therapy
- Referral to structured program
PREDIABETES ALGORITHM

IFG (100–125) | IGT (140–199) | METABOLIC SYNDROME (NCEP 2001)

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

TREAT ASCVD RISK FACTORS

TREAT HYPERGLYCEMIA
FPG >100 | 2-hour PG >140

1 PRE-DM CRITERION

MULTIPLE PRE-DM CRITERIA

NORMAL GLYCEMIA

Progression

TREAT ASCVD RISK FACTOR MODIFICATIONS ALGORITHM

DYSLIPIDEMIA ROUTE

HYPERTENSION ROUTE

1 PRE-DM CRITERION

MULTIPLE PRE-DM CRITERIA

TREAT HYPERGLYCEMIA
FPG >100 | 2-hour PG >140

1 PRE-DM CRITERION

MULTIPLE PRE-DM CRITERIA

If glycemia not normalized

LEGEND

Orlistat, lorcaserin, phentermine/topiramate ER, naltrexone/bupropion, lixisenatide 3 mg, or bariatric surgery as indicated for obesity treatment

PROCEED TO GLYCEMIC CONTROL ALGORITHM

OVERT DIABETES

LOW-RISK MEDICATIONS

Consider with Caution

TZD

GLP-1RA

Acarbose

If glycemia not normalized

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COMPLICATIONS-CENTRIC MODEL FOR CARE OF THE PATIENT WITH OVERWEIGHT/OBESITY

STEP 1: EVALUATION FOR COMPLICATIONS AND STAGING

- **CARDIOMETABOLIC DISEASE**
  - **BMI <25**
    - NO OVERWEIGHT OR OBESITY
  - **BMI ≥25**
    - OVERWEIGHT OR OBESITY

- **BIOMECHANICAL COMPLICATIONS**
  - **BMI ≥25**
    - MILD TO MODERATE
    - SEVERE

**STAGE 0**

**STAGE 1**

**STAGE 2**

STEP 2: SELECT:

- **Therapeutic targets for improvement in complications**
- **Treatment modality**
- **Treatment intensity based on staging**

- **Lifestyle Therapy:** Physician/RD counseling, web/remote program, structured multidisciplinary program

- **Medical Therapy (BMI ≥27):** Individualize care by selecting one of the following based on efficacy, safety, and patients' clinical profile: phentermine, orlistat, lorcaserin, phentermine/topiramate ER, naltrexone/bupropion, liraglutide 3 mg

- **Surgical Therapy (BMI ≥35):** Gastric banding, sleeve, or bypass

STEP 3: If therapeutic targets for complications not met, intensify lifestyle, medical, and/or surgical treatment modalities for greater weight loss. Obesity is a chronic progressive disease and requires commitment to long-term therapy and follow-up.
CMS Finalizes Expanded Diabetes Prevention Program

In its just-released final rule for the 2018 physician fee schedule (PFS), the Centers for Medicare & Medicaid Services (CMS) issued detailed regulations for the expanded model of the Medicare Diabetes Prevention Program (MDPP). Under this expanded model, which builds on an earlier test of MDPP and was announced in 2016, CMS will add MDPP as a covered benefit for Medicare beneficiaries who meet certain criteria, starting on April 1, 2018.

MDPP is designed to supply coaching services to prediabetic patients to help them lose weight and avoid developing type 2 diabetes. Community health workers and health professionals will supply these services in community and healthcare settings.

"The sessions provide practical training in long-term dietary change, increased physical activity, and problem-solving strategies for overcoming challenges to maintaining weight loss and a healthy lifestyle," the final rule said.

The set of MDPP services includes core sessions (first 6 months), core maintenance sessions (second 6 months), and ongoing maintenance sessions (second year). Sixteen weekly sessions must be completed within the first 6 months, when the likelihood of losing weight is greatest.
Individualize

Choose A1c goal

7% for most patients

< 7% younger with few comorbidities

Older group with multiple comorbidities could be around 8%
Glucose-lowering medication in type 2 diabetes: overall approach.
Case 1: Carmen

55 year-old female with newly diagnosed type 2 diabetes

Active: she takes care of her grandchildren while their mother works

Too busy to exercise. Eats the same food as her grandchildren

No alcohol

Has hypertension and sleep apnea

No history of pancreatitis, no abnormal liver function, or CHF

On physical examination, she is alert oriented cooperative no acute distress

Height: 64” Weight 188# BMI=33
BP=160/100
Foot Exam: normal pulses; normal sensory

Fundoscopy, no retinopathy
A1c=7.4%;
creatinine .9 mg/dL;
no microalbuminuria;
LDL=146 mg/dL
Current Medications:
Valsartan 80 mg; Atenolol 50 mg;
HCT 25 po daily

Jorge De Jesús MD FACE
### ASCVD Risk Factor Modifications Algorithm

#### Dyslipidemia

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

- **Lipid Panel:** Assess ASCVD Risk
  - If TG > 500 mg/dL, fibrates, Rx-grade omega-3 fatty acids, niacin

**Statin Therapy**

- If statin-intolerant
  - Try alternate statin, lower statin dose or frequency, or add nonstatin LDL-C-lowering therapies
- Repeat lipid panel; assess adequacy, tolerance of therapy
- Intensify therapies to attain goals according to risk levels

#### Risk Levels

<table>
<thead>
<tr>
<th>Risk Levels</th>
<th>High</th>
<th>Very High</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mg/dL)</td>
<td>&lt;100</td>
<td>&lt;70</td>
<td>&lt;55</td>
</tr>
<tr>
<td>Non-HDL-C (mg/dL)</td>
<td>&lt;130</td>
<td>&lt;100</td>
<td>&lt;80</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>&lt;150</td>
<td>&lt;150</td>
<td>&lt;150</td>
</tr>
<tr>
<td>Apo B (mg/dL)</td>
<td>&lt;90</td>
<td>&lt;80</td>
<td>&lt;70</td>
</tr>
</tbody>
</table>

**If not at desirable levels:**

- Intensify lifestyle therapy (weight loss, physical activity, dietary changes) and glycemic control; consider additional therapy

**To lower LDL-C:**
- Intensify statin, add ezetimibe, PCSK9i, colesvelam, or niacin
- Intensify statin and/or add Rx-grade OM3 fatty acid, fibrate, and/or niacin
- Statin + PCSK9i

**To lower Non-HDL-C, TG:**

**To lower Apo B, LDL-P:**

**To lower LDL-C in FH:**

- Assess adequacy & tolerance of therapy with focused laboratory evaluations and patient follow-up

* Even more intensive therapy might be warranted
** Familial Hypercholesterolemia

#### Hypertension

**Goal:** Systolic < 130, Diastolic < 80 mm Hg

**ACEI or ARB**

- For initial blood pressure > 150/100 mm Hg; DUAL THERAPY
  - ACEi or ARB + Calcium Channel Blocker
  - β-blocker
  - Thiazide

**If not at goal (2–3 months):**

- Add calcium channel blocker, β-blocker or thiazide diuretic

**If not at goal (2–3 months):**

- Add next agent from the above group, repeat

**If not at goal (2–3 months):**

- Additional choices (α-blockers, central agents, vasodilators, aldosterone antagonists)

Achievement of target blood pressure is critical
**Biguanides**

**Metformin**

- **Mechanism**
  - Insulin sensitivity
  - Hepatic glucose production
  - FPG more than PPG

- **Efficacy**
  - A1C 1%-2%

- **Advantages**
  - No weight gain or hypoglycemia, potential weight loss

- **Disadvantages**
  - GI side effects
  - Lactic acidosis *(rare)*

- **Contraindications**
  - Renal disease; CHF

Combinations available with SU, TZD, repaglinide, and DPP-4 inhibitors

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A1C = glycated hemoglobin; CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; GI = gastrointestinal; PPG = post-prandial glucose; SU = sulfonylurea; TZD = thiazolidinedione

*Metformin [package insert]. Princeton NJ; Bristol Myers Squibb; 2009.*
Metformin Background Treatment

- Low risk of Hypoglycemia
- Does NOT promote weight gain
- Good antihyperglycemic efficacy
- Durable effects
- Robust cardiovascular safety
- Vitamin B12 malabsorption and deficiency in 16% of users

- Dosing is adjusted in eGFR
  - Under 30 ml/min:
    - Do NOT use
  - 30-45 ml/min:
    - Do NOT start metformin
    - Adjust to Max dose ~1000mg/day
  - 45-60 ml/min:
    - Can use full dose but monitor renal function every 3-6 months

Garber AJ *Endocrine Practice* 2018; 24:91.
Lipska, KJ *Diabetes Care* 2011;34:1431.
After Metformin what do we use??

What we all struggle with is what to choose as our second medicine, and this is where the new guidelines provide some very clear advice. We start by asking: Does the patient have established cardiovascular (CV) disease, congestive heart failure (CHF), or renal disease? If they do (and that encompasses about 20% of our patients), then we start with either a sodium-glucose cotransporter 2 (SGLT2) inhibitor or a glucagon-like peptide-1 receptor agonist (GLP-1RA) with proven CV benefit. The GLP-1Rs are preferred if someone’s main issue is atherosclerotic heart disease. Evidence of benefit is strongest for liraglutide, favorable for semaglutide, and less certain for exenatide. With the release of the topline results from the REWIND trial, which were issued after the guidelines were published, we now know that dulaglutide has CV benefit in a broad population and is also on the map.
Glucose-lowering medication in type 2 diabetes: overall approach.

**FIRST-LINE** therapy is metformin and comprehensive lifestyle (including weight management and physical activity) if HbA\(_1c\) above target proceed as below

**ESTABLISHED ASCVD OR CKD**

**ASCVD PREDOMINATES**
- GLP-1 RA with proven CVD benefit\(^1\)
- SGLT2i with proven CVD benefit; if eGFR adequate\(^2\)

- If HbA\(_1c\) 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
  - Base insulin\(^4\)
  - TZD\(^5\)

- If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i
  - Choose agents demonstrating CV safety:
    - Consider adding the other class with proven CVD benefit
    - DPP-4i if not on GLP-1 RA
    - Base insulin
    - TZD

**HF OR CKD PREDOMINATES**
- PREFERABLY
  - SGLT2i with evidence of reducing HF and/or CVD progression in CVOTs if eGFR adequate\(^2\)
  - OR
  - GLP-1 RA with proven CVD benefit

- If SGLT2i not tolerated or contraindicated or if eGFR less than adequate/acid GLP-1 RA with proven CVD benefit
  - Avoid TZD in the setting of HF
  - Choose agents demonstrating CV safety:
    - Consider adding the other class with proven CVD benefit
    - DPP-4i if not on GLP-1 RA
  - Base insulin
  - TZD

- If HbA\(_1c\) above target
  - Consider the addition of SU or basal insulin:
    - Choose later generation SU with lower risk of hypoglycemia
    - Consider basal insulin with lower risk of hypoglycemia\(^6\)

**COMPPELLING NEED TO MINIMIZE HYPOGLYCEMIA**
- IF HbA\(_1c\) above target
  - SGLT2i
  - OR
  - TZD

- IF HbA\(_1c\) above target
  - GLP-1 RA
  - OR
  - DPP-4i

- IF HbA\(_1c\) above target
  - SGLT2i
  - OR
  - TZD

**COMPPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS**
- IF HbA\(_1c\) above target
  - GLP-1 RA
  - OR
  - DPP-4i

- IF HbA\(_1c\) above target
  - SGLT2i
  - OR
  - TZD

**COST IS A MAJOR ISSUE**
- IF HbA\(_1c\) above target
  - GLP-1 RA
  - OR
  - DPP-4i

**1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA, evidence for linedalik or endoter is GESH, DPP-4i, SGLT2i, and SP. For SGLT2i, evidence mostly stronger for empagliflozine.**

**2. Be aware that SGLT2i vary in region and individual patient with regard to indicated level of eGFR for initiation and continued use.**

**3. Both empagliflozine and canagliflozine have shown reduction in HF and reduction in CV progression in CVOTs.**

**4. Empagliflozine and canagliflozine have demonstrated CVD safety.**

**5. Low dose may be better tolerated through less well studied for CVD effects.**

**6. Choice later generation SU with lower risk of hypoglycemia.**

**American Diabetes Association Dia Care 2019;42:S90-S102**

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GLP1-RA Increase Active Incretin Levels

Normal Physiology

Active GLP-1

DPP-4

Inactive GLP-1

GLP-1 RA

DPP-4 inhibitor

Resistance

Increased circulating GLP-1 levels

• Increased insulin secretion
• Decreased glucagon release

Glucose control improved

Exenatide (Byetta-Bydureon)
Liraglutide (Vyctoza)
Dulaglutide (Trulicity)
Lixisenatide
Semaglutide (Ozempic)

GLP-1 = glucagon-like peptide-1; GLP1-RA = glucagon-like peptide-1 receptor agonist; DPP-4 = dipeptidyl peptidase 4

Umpierrez et al. Endocrine Practice 2014
## Reduction in CV Death, Nonfatal MI, and Nonfatal Stroke With Some GLP-1 Receptor Agonists

<table>
<thead>
<tr>
<th></th>
<th>LEADER (liraglutide)</th>
<th>SUSTAIN-6 (semaglutide)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 9340[a]</td>
<td>N = 3297[b]</td>
</tr>
<tr>
<td>Primary composite endpoint</td>
<td>CV death, MI, or stroke</td>
<td>CV death, MI, or stroke</td>
</tr>
<tr>
<td></td>
<td>HR = 0.87 (0.78, 0.97)</td>
<td>HR = 0.74 (0.58, 0.95)</td>
</tr>
<tr>
<td></td>
<td><em>P</em> &lt; .001 for noninferiority</td>
<td><em>P</em> &lt; .001 for noninferiority</td>
</tr>
<tr>
<td></td>
<td><em>P</em> = .01 for superiority</td>
<td><em>P</em> = .02 for superiority</td>
</tr>
<tr>
<td>CV death</td>
<td>0.78 (0.66, 0.93)</td>
<td>0.98 (0.65, 1.48)</td>
</tr>
<tr>
<td></td>
<td><em>P</em> = .007</td>
<td><em>P</em> = .92</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>0.86 (0.73, 1.00)</td>
<td>0.74 (0.51, 1.08)</td>
</tr>
<tr>
<td></td>
<td><em>P</em> = .046</td>
<td><em>P</em> = .12</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>0.86 (0.71, 1.06)</td>
<td>0.61 (0.38, 0.99)</td>
</tr>
<tr>
<td></td>
<td><em>P</em> = .16</td>
<td><em>P</em> = .04</td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>0.87 (0.73, 1.05)</td>
<td>1.11 (0.77, 1.61)</td>
</tr>
<tr>
<td></td>
<td><em>P</em> = .14</td>
<td><em>P</em> = .57</td>
</tr>
</tbody>
</table>

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GLP-1 RA limitations and special considerations

- Nausea
- ... pancreatitis
- ...MTC and associated multiple endocrine neoplasia
- ...renal for exenatide
- ... parenterals
Glucose-lowering medication in type 2 diabetes: overall approach.
Overview on the Predominant Distribution of SGLT1 and SGLT2 Receptors Along the Nephron

Reabsorption

SGLT2

SGLT1

Distal S2/S3 segment of proximal tubule

Collecting duct

Normal glucose < 65 mg/d
180 g glucose = 720 kcal

SGLT2 Inhibitors

• Mechanism of action:
  • Decrease re-absorption of glucose in the proximal convoluted tubule
  • Decrease renal threshold so urinary glucose excretion occurs at lower plasma glucose concentration

• FDA-approved
  • Canagliflozin
  • Dapagliflozin
  • Empagliflozin
  • Ertugliflozin

FDA = U.S. Food and Drug Administration; SGLT-2 = sodium-dependent glucose cotransporters-2.
Bays, H. Diabetes Therapy, 2013.
Among SGLT2s, we have excellent outcome data on empagliflozin and canagliflozin, both of which are mentioned in the guidelines. But things are happening quickly. After the guidelines came out, the DECLARE trial\textsuperscript{[3]} results, looking at dapagliflozin, were published. That trial did not show a lower rate of MACE (major adverse cardiovascular events) with dapagliflozin, but treatment with the drug did result in a lower rate of CV death or hospitalization for heart failure. So the SGLT2s are also on the map.

Empagliflozin—Jardiance
Canagliflozin—Invokana
Dapagliflozin—Farxiga
# EMPA-REG OUTCOME and CANVAS CVOTs

<table>
<thead>
<tr>
<th>CVOT</th>
<th>Patient Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME(^{(a)})</td>
<td>99% of patients had prior CV event (obstructive coronary lesions or revascularization, nonfatal MI, nonfatal stroke, evidence of occlusive peripheral vascular disease)</td>
</tr>
<tr>
<td>N = 7020</td>
<td></td>
</tr>
<tr>
<td>CANVAS, CANVAS-R(^{(b)})</td>
<td>33% of patients at risk for CV events</td>
</tr>
<tr>
<td>N = 10142</td>
<td>66% of patients had established CV events</td>
</tr>
</tbody>
</table>

3-point MACE: nonfatal MI, nonfatal stroke, and CV death\(^{(a,b)}\)

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EMPA-REG OUTCOME CV Outcome Trial: Empagliflozin Reduced CV Mortality

Primary Outcome:
- Empagliflozin (n = 4687)
- Placebo (n = 2333)
- HR = 0.86 (95% CI: 0.74, 0.99)
- P = .04 for superiority

Death From CV Causes:
- HR = 0.62 (95% CI: 0.49, 0.77)
- P < .001

Death From Any Cause:
- HR = 0.68 (95% CI: 0.57, 0.82)
- P < .001

Hospitalization for HF:
- HR = 0.65 (95% CI: 0.50, 0.85)
- P = .002

FDA News Release:
FDA approves Jardiance to reduce cardiovascular death in adults with type 2 diabetes

Study links Jardiance to improved survival in patients with type 2 diabetes with cardiovascular disease
Canagliflozin Reduced MACE Similarly to Empagliflozin in the CANVAS CV Outcome Trial

<table>
<thead>
<tr>
<th></th>
<th>CANVAS[a] (canagliflozin)</th>
<th>EMPA-REG OUTCOME[b] (empagliflozin)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 10,142</td>
<td>N = 7034</td>
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<tr>
<td>Primary composite endpoint</td>
<td>CV death, nonfatal MI, or nonfatal stroke</td>
<td>CV death, MI, or stroke</td>
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<tr>
<td></td>
<td>HR = 0.86 (0.75, 0.97)</td>
<td>HR = 0.86 (0.74, 0.99)</td>
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<td>P &lt; .001 for noninferiority</td>
<td>P &lt; .001 for noninferiority</td>
</tr>
<tr>
<td></td>
<td>P = .02 for superiority</td>
<td>P = .04 for superiority</td>
</tr>
<tr>
<td>CV death</td>
<td>0.87 (0.72, 1.06)</td>
<td>0.62 (0.49, 0.77)</td>
</tr>
<tr>
<td></td>
<td>P &lt; .001</td>
<td></td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>0.85 (0.69, 1.05)</td>
<td>0.87 (0.70, 1.09)</td>
</tr>
<tr>
<td></td>
<td>P = .23</td>
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<tr>
<td>Nonfatal stroke</td>
<td>0.90 (0.71, 1.15)</td>
<td>1.24 (0.92, 1.67)</td>
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<tr>
<td></td>
<td>P = .16</td>
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<tr>
<td>Hospitalization for UA</td>
<td>--</td>
<td>0.99 (0.74, 1.34)</td>
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<tr>
<td></td>
<td></td>
<td>P = .97</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>0.67 (0.52, 0.87)</td>
<td>0.65 (0.50, 0.85)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P = .002</td>
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</table>

Canaglifozin New Approved Indications *

Indicated as adjunct to diet and exercise to improve glycemic events in adults with Type 2 Diabetes Mellitus

Indicated to reduce major adverse cardiovascular events

Cardiovascular Death, Non fatal Myocardial Infarction, non fatal stroke
In adults with Type 2 Diabetes Mellitus and established cardiovascular disease

Canaglifozin (Invokana) Package Insert.
## DECLARE-TIMI58 and VERTIS-CV

### Demographics

<table>
<thead>
<tr>
<th>DECLARE-TIMI58 (dapagliflozin)</th>
<th>VERTIS-CV (ertugliflozin)</th>
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<tbody>
<tr>
<td><strong>Total</strong> (N = 17,160)</td>
<td><strong>Total</strong> (N = 8237)</td>
</tr>
<tr>
<td><strong>CVD</strong> (n = 6971)</td>
<td><strong>CVD</strong></td>
</tr>
<tr>
<td><strong>Multiple Risk Factors</strong> (n = 10,189)</td>
<td><strong>Multiple Risk Factors</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Men, n (%)</th>
<th>Mean age, y (± SD)</th>
<th>Mean HbA₁c (%)</th>
<th>Cardiac history, n (%) HF</th>
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<tbody>
<tr>
<td><strong>DECLARE-TIMI58</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total (N = 17,160)</td>
<td>10738 (62.6)</td>
<td>63.8 (6.8)</td>
<td>9.7</td>
<td>1698 (9.9)</td>
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<tr>
<td>CVD (n = 6971)</td>
<td>5023 (72.1)</td>
<td>62.5 (8.1)</td>
<td>9.7</td>
<td>1133 (16.3)</td>
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<tr>
<td>Multiple Risk Factors (n = 10,189)</td>
<td>5715 (56.1)</td>
<td>64.7 (5.6)</td>
<td>9.7</td>
<td>565 (5.5)</td>
</tr>
<tr>
<td><strong>VERTIS-CV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (N = 8237)</td>
<td>5763 (70.0)</td>
<td>64.4</td>
<td>8.3</td>
<td></td>
</tr>
</tbody>
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Higher Risk for Amputations in Patients Taking Canagliflozin

- 2-fold excess risk for amputations in patients who take canagliflozin compared with placebo
- ~180 amputations, 71% of those amputations were toes and metatarsal bones
- 3 independent risk factors for amputation identified across CANVAS program, whether the participant received canagliflozin or placebo

Exert caution in people who have 1) a prior amputation, 2) neuropathy, or 3) PVD; canagliflozin may not be the best antihyperglycemic agent in these situations

EMPA-REG OUTCOME and CANVAS
Lower Limb Amputations

- CANVAS, CANVAS-R
- 92% of the patients who eventually had an amputation, a premorbid event of either an infection or an ulcer was identified

Perform foot exams and discuss foot care

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

Abstract

BACKGROUND The cardiovascular safety profile of dapagliflozin, a selective inhibitor of sodium–glucose cotransporter 2 that promotes glucosuria in patients with type 2 diabetes, is undefined.

METHODS We randomly assigned patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease to receive either dapagliflozin or placebo. The primary safety outcome was a composite of major adverse cardiovascular events (MACE), defined as cardiovascular death, myocardial infarction, or ischemic stroke. The primary efficacy outcomes were MACE and a composite of cardiovascular death or hospitalization for heart failure. Secondary efficacy outcomes were a renal composite (≥40% decrease in estimated glomerular filtration rate to <60 ml per minute per 1.73 m² of body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes) and death from any cause.

CONCLUSIONS In patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease, treatment with dapagliflozin did not result in a higher or lower rate of MACE than placebo but did result in a lower rate of cardiovascular death or hospitalization for heart failure, a finding that reflects a lower rate of hospitalization for heart failure. (Funded by AstraZeneca; DECLARE–TIMI 58 ClinicalTrials.gov number, NCT01730534.)
Diabetes and HF

- Diabetes is a major risk factor for incident HF
- Diabetes is very common in prevalent HF
- HF is the most disabling and deadly complication of diabetes – patients with both conditions do especially badly
- Therapies for HF are effective in patients with diabetes
Diabetes and Incident HF in the United States

- Framingham study: the risk of development of HF in increased by:\[a\]
  - $2 \times$ in diabetic males
  - $5 \times$ in diabetic females
  - $4 \times$ in diabetic males $\leq 65$ years
  - $8 \times$ in young diabetic females

- US HMO prevalence study:\[b\]
  - With diabetes, incident HF developed at a rate of 3.3% per year

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5-Year Kaplan–Meier Survival Estimates for 115,803 Adults Aged 65 Years With Diabetes by Incident HF
Importance of Real-World Data

• Complement clinical trial data\[a\]
• Real-world data provide evidence of the effect of a health care intervention in clinical practice\[a\]
• Clinicians need to understand how to interpret clinical trial and real-world data

"Real-world evidence can inform therapeutic development, outcomes research, patient care, research on healthcare systems, quality improvement, safety surveillance, and well-controlled effectiveness studies.\[b]\"

CVD-REAL Study: Real-World Data Evaluating SGLT2 Inhibitors

- Assessed data from 309,056 patients with T2D in 6 countries
- Treatment with SGLT2 inhibitors (dapagliflozin, canagliflozin, and empagliflozin) associated with a 39% reduction in the rate of hospitalization for heart failure
- Directionally similar decreases in all-cause death

Practice Essentials

Diabetic nephropathy is a clinical syndrome characterized by the following:

- Persistent albuminuria (>300 mg/d or >200 µg/min) that is confirmed on at least 2 occasions 3-6 months apart
- Progressive decline in the glomerular filtration rate (GFR)
- Elevated arterial blood pressure
# Cardiorenal Benefit With SGLT2 Inhibitors

<table>
<thead>
<tr>
<th>CANVAS[^a] (canagliflozin) N = 10,142</th>
<th>EMPA-REG OUTCOME[^b] (empagliflozin) N = 7034</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progression of albuminuria</strong></td>
<td>Incident or worsening nephropathy or CV death</td>
</tr>
<tr>
<td>0.73 (0.67, 0.79)</td>
<td>0.61 (0.55, 0.69)</td>
</tr>
<tr>
<td><strong>Composite of 40% reduction in eGFR, ESRD, or renal death</strong></td>
<td>Doubling of serum creatinine level accompanied by eGFR of ≤ 45 mL/min/1.73 m²</td>
</tr>
<tr>
<td>0.60 (0.47, 0.77)</td>
<td>0.56 (0.39, 0.79)</td>
</tr>
<tr>
<td><strong>Regression of albuminuria</strong></td>
<td>Initiation of renal replacement therapy</td>
</tr>
<tr>
<td>1.70 (1.51, 1.91)</td>
<td>0.45 (0.21, 0.97)</td>
</tr>
</tbody>
</table>

Exploring the Potential Renal Benefits of Canagliflozin

Progression of Albuminuria

- Canagliflozin: HR = 0.73 (95% CI: 0.67, 0.79)
- Placebo

Regression of Albuminuria

- Canagliflozin: HR = 1.70 (95% CI: 1.51, 1.91)
- Placebo

~70% of the patients in CANVAS had normal renal function and not micro- or macro-albuminuria

Special considerations for SGLT-2

• Hypotension
• Volume depletion
• Genital mycotic infections
• Hyperkalemia
• Fractures (upper extremities first 12 weeks canaglifozin)
• “euglycemic DKA” (case selection important)
• Fournier gangrene (rare)
• Amputations lower limb (canaglifozin)
Raúl: Taxi Driver; age 54
T2DM x 7 years

Lack of adherence due to hypoglycemic episodes; refuses injections; concerned frequent urination due to his type of work

Glimepiride 2 mg po once daily
Metformin 1000 mg po bid

A1c=7.6%

Table 2. Raul's Clinical Presentation and Blood Test Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Result/Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height</td>
<td>175 cm</td>
</tr>
<tr>
<td>Weight</td>
<td>85.7 kg</td>
</tr>
<tr>
<td>BMI</td>
<td>28 kg/m²</td>
</tr>
<tr>
<td>Heart rate</td>
<td>80 beats/min</td>
</tr>
<tr>
<td>Blood pressure (left arm)</td>
<td>130/80 mm Hg</td>
</tr>
<tr>
<td>Skin</td>
<td>Normal</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Persistent mild numbness and tingling in legs</td>
</tr>
<tr>
<td>Eye</td>
<td>Dilated fundus exam indicates early retinopathy</td>
</tr>
<tr>
<td>HbA1c</td>
<td>7.6%</td>
</tr>
<tr>
<td>Mean fasting plasma glucose</td>
<td>126 mg/dL (range: 115-140)</td>
</tr>
<tr>
<td>Mean postprandial plasma glucose</td>
<td>160 mg/dL (range: 140-200)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>90 mg/dL</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>44 mg/dL</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>240 mg/dL</td>
</tr>
<tr>
<td>eGFR</td>
<td>&gt;90 mL/min/1.73 m²</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>0.7 mg/dL</td>
</tr>
</tbody>
</table>

BMI = body mass index; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; eGFR = estimated glomerular filtration rate.

Jorge De Jesus MD FACE
Rationale for using Incretin-Based Therapies in the Treatment of T2 DM in this case

• A-Incretins play an important role in glucose homeostasis
• B-Incretin Effects are Diminished in T2DM
• C-Incretin based therapies (GLP-1RA and DPP4 inhibitors)
• D-Target multiple defects in DM type 2, not addressed by traditional medications
• E-Not associated with hypoglycemia
• F-Either weight neutral or can cause weight loss (GLP-1 RA)
DPP-4 Inhibitors

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade Name</th>
<th>FDA Approval</th>
<th>CV Safety Study</th>
<th>GoodRx</th>
<th>Medical Letter</th>
<th>Cost per Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopgliptin</td>
<td>Nesina™</td>
<td>Jan 2013</td>
<td>Oct 2013&lt;sup&gt;a&lt;/sup&gt;</td>
<td>$95</td>
<td>$312</td>
<td></td>
</tr>
<tr>
<td>Linagliptin</td>
<td>Tradjenta™</td>
<td>May 2011</td>
<td>May 2019</td>
<td>$356</td>
<td>$331</td>
<td></td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>Onglyza™</td>
<td>Jul 2009</td>
<td>Oct 2013&lt;sup&gt;b&lt;/sup&gt;</td>
<td>$394</td>
<td>$325</td>
<td>$13/day</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>Januvia™</td>
<td>Oct 2006</td>
<td>Jul 2015&lt;sup&gt;c&lt;/sup&gt;</td>
<td>$427</td>
<td>$331</td>
<td></td>
</tr>
</tbody>
</table>

- Omarigliptin is an oral once weekly DPP-4 inhibitor NOT FDA approved but used in Japan.
  - Completed CVOT with results similar to above and without HF noise

GoodRx accessed on Jan 20, 2018
<sup>a</sup>NEJM 2015;373:232
<sup>b</sup>NEJM 2013;369:1317
<sup>c</sup>Cardiovasc. Diabetol. 2017 Sep 11;16(1):112
Some DPP-4 Inhibitors Increase Risk of Hospitalization for Heart Failure

<table>
<thead>
<tr>
<th></th>
<th>SAVOR-TIMI 53[^a] (saxagliptin)</th>
<th>EXAMINE[^b] (alogliptin)</th>
<th>TECOS[^c] (sitagliptin)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 16,492</td>
<td>N = 5380</td>
<td>N = 14,671</td>
</tr>
<tr>
<td>Primary composite endpoint</td>
<td>CV death, MI, or stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR = 1.00 (0.89, 1.12)</td>
<td>HR = 0.96 (≤ 1.16)</td>
<td>CV death, MI, stroke,</td>
</tr>
<tr>
<td></td>
<td>P = .99 for superiority</td>
<td>P = .32 for superiority</td>
<td>or hospitalization for</td>
</tr>
<tr>
<td></td>
<td>P &lt; .001 for noninferiority</td>
<td>P &lt; .001 for noninferiority</td>
<td>UA</td>
</tr>
<tr>
<td></td>
<td>HR = 0.98 (0.89, 1.08)</td>
<td></td>
<td>HR = 0.98 (0.83, 1.20)</td>
</tr>
<tr>
<td></td>
<td>P = .65</td>
<td></td>
<td>P = .65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = .98</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>1.27 (1.07, 1.51)</td>
<td>1.07 (0.79, 1.46)</td>
<td>1.00 (0.83, 1.20)</td>
</tr>
<tr>
<td></td>
<td>P = .007</td>
<td>P = .657[^d]</td>
<td>P = .98</td>
</tr>
</tbody>
</table>

- FDA has updated labels for products containing saxagliptin and alogliptin to include warning about heart failure
- CAROLINA (linagliptin) study is ongoing

# Profiles of Antidiabetic Medications

<table>
<thead>
<tr>
<th></th>
<th>MET</th>
<th>GLP1-RA</th>
<th>SGLT2i</th>
<th>DPP4i</th>
<th>AGi</th>
<th>TZD (moderate dose)</th>
<th>SU</th>
<th>GLN</th>
<th>COLSvl</th>
<th>BCR-QR</th>
<th>INSULIN</th>
<th>PRAML</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYPO</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate to Severe</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>Slight Loss</td>
<td>Loss</td>
<td>Loss</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Loss</td>
</tr>
<tr>
<td>RENAL / GU</td>
<td>Contra-indicated if eGFR &lt;30 mL/min/1.73 m²</td>
<td>Not Indicated for eGFR &lt;45 mL/min/1.73 m²</td>
<td>Genital Mycotic Infections</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td></td>
</tr>
<tr>
<td>GI Sx</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Mild</td>
<td>Moderate</td>
<td>Neutral</td>
</tr>
<tr>
<td>CHF</td>
<td>Neutral</td>
<td>See #1</td>
<td>See #2</td>
<td>See #3</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>CHF Risk</td>
<td></td>
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<tr>
<td>ASCVD</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Mild Fracture Risk</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td></td>
</tr>
<tr>
<td>BONE</td>
<td>Neutral</td>
<td>Neutral</td>
<td>DKA Can Occur in Various Stress Settings</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td></td>
</tr>
<tr>
<td>KETOACIDOSIS</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td></td>
</tr>
</tbody>
</table>

**Key:**
- Green: Few adverse events or possible benefits
- Orange: Use with caution
- Red: Likelihood of adverse effects

1. Liraglutide—FDA approved for prevention of MACE events.
2. Empagliflozin—FDA approved to reduce CV mortality. Canagliflozin—FDA approved to reduce MACE events.
3. Possible increased hospitalizations for heart failure with alogliptin and saxagliptin.
4. Only empagliflozin and canagliflozin show CVD and CKD benefits.
5. Liraglutide only shows CVD and CKD benefits.

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**Algorithm for Adding/Intensifying Insulin**

**Start Basal** (Long-Acting Insulin)

- **A1C < 8%**
  - TDD: 0.1–0.2 U/kg
- **A1C > 8%**
  - TDD: 0.2–0.3 U/kg

**Insulin Titration every 2–3 days to reach glycemic goal:**

- **Fixed regimen:** Increase TDD by 2 U
- **Adjustable regimen:**
  - FBG > 180 mg/dL: add 20% of TDD
  - FBG 140–180 mg/dL: add 10% of TDD
  - FBG 110–139 mg/dL: add 1 unit
  - If hypoglycemia, reduce TDD by:
    - BG < 70 mg/dL: 10% – 20%
    - BG < 40 mg/dL: 20% – 40%

**Consider discontinuing or reducing sulfonylurea after starting basal insulin (basal analogs preferred to NPH)**

**Intensify** (Prandial Control)

- **Add GLP1-RA**
  - Or SGLT2i
  - Or DPP4i
- **Add Prandial Insulin**
  - Basal Plus 1, Plus 2, Plus 3
  - Basal Bolus

**Glycemic Control Not at Goal***

**Insulin Titration every 2–3 days to reach glycemic goal:**

- Increase prandial dose by 10% or 1–2 units if 2-h postprandial or next premeal glucose consistently > 140 mg/dL
- If hypoglycemia, reduce TDD basal and/or prandial insulin by:
  - BG consistently < 70 mg/dL: 10% – 20%
  - Severe hypoglycemia (requiring assistance from another person) or BG < 40 mg/dL: 20% – 40%

**Glycemic Goal:**

- < 7% for most patients with T2D; fasting and premeal
- BG < 110 mg/dL; absence of hypoglycemia
- A1C and FBG targets may be adjusted based on patient's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk

*Glycemic Goal:

- < 7% for most patients with T2D; fasting and premeal
- BG < 110 mg/dL; absence of hypoglycemia
- A1C and FBG targets may be adjusted based on patient's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk

**Basal Plus 1, Plus 2, Plus 3**

- Begin prandial insulin before largest meal
- If not at goal, progress to injections before 2 or 3 meals
- Start: 10% of basal dose or 5 units

**Basal Bolus**

- Begin prandial insulin before each meal
- 50% Basal / 50% Prandial TDD 0.3–0.5 U/kg
- Start: 50% of TDD in three doses before meals
Combination of Basal Insulin with a GLP-1 Agonist Has a Scientific Logic

Basal insulin analogs:
- Simple to initiate
- Control nocturnal and FPG
- Lower hypoglycaemia risk vs NPH
- Modest weight increase (1–3 kg)
- Achieve A1C targets in ~50–60%

GLP-1 agonists:
- Simple to initiate
- Pronounced PPG control
- No increase in hypoglycaemia
- Weight lowering/neutral effects
- Achieve A1C targets in ~40–60%

Complementary actions
Additive effects
Fixed Formulation

LixiLan* – fixed-ratio formulation glargine with lixisenatide in a single-pen device

February 28, 2019

Soliqua 100/33 Indication Expanded to Include T2D Patients Uncontrolled on Oral Antidiabetic Agents

Soliqua*
### IDegLira* vs Glargine

#### Comparison of Efficacy and Safety in DUAL V

<table>
<thead>
<tr>
<th></th>
<th>IDegLira* (N = 278)</th>
<th>Glargine (N = 279)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean HbA$_1c$ at randomization, %</td>
<td>8.4</td>
<td>8.2</td>
<td>-</td>
</tr>
<tr>
<td>Mean HbA$_1c$ at wk 26, %</td>
<td>6.6</td>
<td>7.1</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>HbA$_1c$ change at wk 26, %</td>
<td>-1.8</td>
<td>-1.1</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>HbA$_1c$ &lt; 7% at wk 26, %</td>
<td>71.6</td>
<td>47.0</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Body weight at baseline, kg</td>
<td>88.3</td>
<td>87.3</td>
<td>-</td>
</tr>
<tr>
<td>Body weight at wk 26, kg</td>
<td>86.9</td>
<td>89.1</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Body weight change at wk 26, kg</td>
<td>-1.4</td>
<td>+1.8</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Hypoglycemia rate, events/patient year of exposure</td>
<td>2.23</td>
<td>5.05</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Confirmed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nocturnal</td>
<td>0.22</td>
<td>1.23</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

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**Xultophy**