MHIF FEATURED STUDY:  
Rhapsody

**DESCRIPTION:**
First multinational, phase 3, double-blinded, placebo-controlled, randomized withdrawal, study assessing the efficacy of rilonacept, an interleukin 1 alpha and beta receptor decoy, in the treatment of recurrent pericarditis.

**CRITERIA LIST/ QUALIFICATIONS:**

**Inclusion**
Diagnosis of recurrent pericarditis

**Exclusion**
• Pericarditis secondary to specific prohibited etiologies, including tuberculosis (TB); neoplastic, purulent, or radiation etiologies
• Post-thoracic blunt trauma (e.g., motor vehicle accident)
• Myocarditis
• Systemic autoimmune diseases with exception of Still’s disease, pregnancy, hx HIV, prednisone > 60 mg/day, positive Hep B or C, serious infection

<table>
<thead>
<tr>
<th>CONDITION:</th>
<th>PI:</th>
<th>RESEARCH CONTACT:</th>
<th>SPONSOR:</th>
</tr>
</thead>
</table>
| Pericarditis | David Lin, MD | Christine Majeski  
Christine.Majeski@allina.com | Kiniksa Pharmaceuticals |

MHIF was first in the world to enroll in this trial and has 5 subjects enrolled. Pericarditis patients are experiencing significant benefits and most often have no chest pain after starting this medication.
Minneapolis Heart Institute Foundation® Cardiovascular Grand Rounds

Title: Cardiovascular Risk Reduction and the Role of New Antidiabetic Pharmacotherapies

Speakers: Matthew Lillyblad, PharmD, BCCCP, BCPS-AQ Cardiology
Clinical Pharmacy Coordinator-Cardiology/Critical Care at Abbott Northwestern Hospital
Michael D. Miedema, MD, MPH
Director of Cardiovascular Prevention
Minneapolis Heart Institute® at Abbott Northwestern Hospital

Date: November 4th, 2019
Time: 7:00 - 8:00 AM
Location: Minneapolis Heart Institute Building, Suite 100, Learning Center

OBJECTIVES
At the completion of this activity, the participants should be able to:
1. Outline recent advancements in cardiovascular risk reduction with new diabetic medications.
2. Understand the benefits and risks of SGLT2 inhibitors and GLP-1 agonists in patients with diabetes.
3. Identify patients most likely to benefit from treatment with SGLT2 inhibitors and GLP-1 agonists.

ACCREDITATION
Physician - Allina Health is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. Allina Health designates this live activity for a maximum of 1.0 AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Nurse - This activity has been designed to meet the Minnesota Board of Nursing continuing education requirements for 1.0 hours of credit. However, the nurse is responsible for determining whether this activity meets the requirements for acceptable continuing education.

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Allina Health, Learning & Development intends to provide balance, independence, objectivity and scientific rigor in all of its sponsored educational activities. All speakers and planning committee members participating in sponsored activities and their spouse/partner are required to disclose to the activity audience any real or apparent conflict(s) of interest related to the content of this conference.

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Moderator(s)/Speaker(s)
Matthew Lillyblad and Dr. Michael Miedema have disclosed that they DO NOT have any real or apparent conflicts with any commercial interest as it relates to presenting the content in this activity/course.
Planning Committee
Dr. Alex Campbell, Jake Cohen, Jane Fox, Dr. Kevin Harris, Dr. Kasia Hryniewicz, Rebecca Lindberg, Amy McMeans, Dr. Michael Miedema, Dr. JoEllyn Moore, Pamela Morley, Dr. Scott Sharkey, Maia Hendel and Jolene Bell Makowesky have disclosed that they DO NOT have any real or apparent conflicts with any commercial interest as it relates to the planning of this activity/course. Dr. Mario Gössl has disclosed the following relationships - Edwards Life Sciences: Grant/Research Support; Abbott Vascular, Caisson: Consultant; Speaker’s Bureau: Edwards Lifesciences. Dr. David Hurrell has disclosed the following relationship -Boston Scientific: Chair, Clinical Events Committee.

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If audited by a licensing board or submitting for license renewal or certification renewal, boards will ask you not the entity providing the education for specific information on each activity you are using for credit. You will need to demonstrate that you attended the activity with a copy of your certificate/evidence of attendance, a brochure/flier and/or the conference handout.

Each attendee at an activity is responsible for determining whether an activity meets their requirements for acceptable continuing education and should only claim those credits that he/she actually spent in the activity.

Maintaining these details are the responsibility of the individual.

PLEASE SAVE A COPY OF THIS FLIER AS YOUR CERTIFICATE OF ATTENDANCE.

Signature: ____________________________________________________________________________

My signature verifies that I have attended the above stated number of hours of the CME activity.

Allina Health - Learning & Development - 2925 Chicago Ave - MR 10701 - Minneapolis MN 55407
Type II Diabetes Mellitus: Time for Cardiology to Get Back in the Game

Michael D Miedema MD MPH
Director of Cardiovascular Prevention
Minneapolis Heart Institute and Foundation
November 4th, 2019

68 y/o Male – Annual Follow-up

• Past Medical History
  • Type 2 Diabetes
    • Hgb A1C 7.2%
    • On Metformin 1000mg bid and 33 units of Lantus qAM
  • Hypertension
    • On Amlodipine
  • Dyslipidemia
    • Complicated by statin intolerance
    • On ezetimibe
  • Subclinical coronary atherosclerosis
    • CAC score of 1,218 in 2016
    • No clinical history of ASCVD
68 y/o Male – Annual Follow-up

• Subjective
  • Denies any SOB, chest pain, or exertional symptoms
  • Rides an exercise bike 5-6 times per week for 45 minutes
  • Working on increased intake of fruits/vegetables, less simple carbohydrates
  • Only complaint is weight gain despite diet/exercise (up 5 pounds from last visit)

• ROS
  • Negative

• Social Hx
  • Non-smoker, retired lawyer, married with 3 kids and 6 grandchildren

• Family Hx
  • Father had T2D but no family history of premature CVD

68 y/o Male – Annual Follow-up

• Exam
  • HR 72, BP 128/76, RR 16, O2 Sat 97%, 5’4”, 176 pounds, BMI 30.1
  • Gen: NAD, pleasant
  • Pulm: CTA bilaterally
  • CV: RRR, no murmur, no LE edema
  • GI: Soft and non-tender
  • Skin: No rash
  • Neuro: Alert oriented
68 y/o Male – Annual Follow-up

• Labs
  • Total Cholesterol 171, Trig’s 156, HDL 35, LDL 71
  • Creatinine 0.8, K 4.4
  • Hgb A1C 7.2%

• Imaging
  • Echo 07/2018: Normal LV and RV function, mild left atrial enlargement, no significant valve disease
  • 2016 CAC score: 1,218

Assessment

• Type 2 Diabetes
  • Borderline control

• Hypertension
  • Well controlled

• Hyperlipidemia
  • Reasonably controlled

• Obesity
  • Grade 1
  • Ongoing issues with weight gain

• ASCVD Risk
  • 10-year ASCVD risk 34.1%
  • Known atherosclerosis
    • CAC score 1,218
  • MESA 10-year CHD Risk
    • Without CAC 21.0%
    • With CAC 32.1%
Plan?

- What would you do to address the patient’s diabetes and elevated ASCVD risk?

Diabetes is a major risk factor for CVD

Figure 1. Kaplan–Meier Estimates of the Probability of Death from Coronary Heart Disease in 1059 Subjects with Type 2 Diabetes and 1378 Nondiabetic Subjects with and without Prior Myocardial Infarction. MI denotes myocardial infarction. 1 bars indicate 95 percent confidence intervals.

Haffner et al. NEJM 1998
Diabetes is a major risk factor for CVD

Benjamin et al. 2018 AHA Stats

Prevalence of Diabetes Mellitus

- ~12% of US Adults
- Significant heterogeneity across demographics (Figure)
- Type 2 DM accounts for 90-95% of all cases of DM in the US
- ~34% (81.6 million US adults) have pre-diabetes

Age-adjusted Prevalence of physician diagnosed diabetes mellitus in adults ≥ 20 years of age by race/ethnicity and years of education (NHANES 2011-2014).
4 Key Recommendations

• Nutrition
• Physical Activity
• Metformin
• SGLT-2 and GLP-1 Medications

Nutritional Risk Factors For T2D
**Effect of the DASH Diet on Glycemic Control in Patient with T2D**

Change in Hgb A1C: -0.5 +/- 0.02% vs -1.7% +/- 0.1%, p-value 0.04

Azadbakht L, et al, Diabetes Care 2011

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**Primary Prevention of Cardiovascular Disease with a Mediterranean Diet**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Combined Mediterranean Diets</th>
<th>Control Diet</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>107/2178</td>
<td>64/987</td>
<td>0.69 (0.51-0.94)</td>
<td>0.62</td>
</tr>
<tr>
<td>Female</td>
<td>72/2819</td>
<td>45/1463</td>
<td>0.73 (0.50-1.07)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70 yr</td>
<td>86/3272</td>
<td>47/1504</td>
<td>0.73 (0.52-1.05)</td>
<td>0.84</td>
</tr>
<tr>
<td>≥70 yr</td>
<td>93/1725</td>
<td>62/946</td>
<td>0.71 (0.51-0.98)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>58/2572</td>
<td>40/1261</td>
<td>0.67 (0.45-1.01)</td>
<td>0.63</td>
</tr>
<tr>
<td>Yes</td>
<td>121/2425</td>
<td>69/1189</td>
<td>0.71 (0.53-0.96)</td>
<td></td>
</tr>
</tbody>
</table>
Diabetes Recommendation #1

For all adults with T2DM, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors.

Physical Activity
Effects of Exercise on Glycemic Control in Type 2 Diabetes Mellitus

- Baseline: 0.08% (95% CI -0.29 to 0.45)
- Post: -0.66% (95% CI -0.98% to -0.34%)

Meta-analysis of 504 participants in 14 studies

Boule et al. JAMA 2001

Effects of Aerobic, Resistance, and Combined Training on Glycemic Control in Type 2 Diabetes

- Hemoglobin A1C (%)
- Control, Aerobic, Resistance, Combined
- Baseline, 3 Months, 6 Months

Diabetes Recommendation #2

Adults with T2DM should perform at least 150 minutes per week of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors.

CENTRAL ILLUSTRATION: Healthy Lifestyle and Cardiovascular Disease (CVD) Events Among Diabetic Patients

Metformin

Effect of metformin in overweight patients with type 2 diabetes

UKPDS 34
- 32% reduction in Diabetes-Related Outcomes
- 42% reduction in Diabetes-related death
- 36% reduction in All-cause Mortality

UKPDS 34, Lancet 1998
The overall data support metformin as first-line therapy in type II DM:
- More significant improvements in A1C
- No associated weight gain
- Less Hypoglycemia
- Better CVD outcomes (compared to sulfonylureas and insulin)

For adults with T2DM, it is reasonable to initiate metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk.
Intensive Glucose Control ≠ Reduced CVD Events

**ACCORD – Primary Outcome**

- Patients with Events (%)
- Years

**ACCORD – ALL-Cause Mortality**

- Patients with Events (%)
- Years

10,251 Patients followed for 3.5 years,
A1C 6.4% vs 7.5%

ACCORD Trial, NEJM 2008

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The Association of Intensive Glucose Control with Weight Gain

Percentage of patient with at least 10 kg weight gain over 3.5 years of follow-up in ACCORD

- Standard Control
- Intensive Control

10,251 Patients followed for 3.5 years,
A1C 6.4% vs 7.5%

ACCORD Trial, NEJM 2008
SGLT-2 and GLP-1 Medications

SGLT-2 Inhibitors

- Reduction in Hgb A1C ~0.5-0.6%
- Decreased body weight
- Decreased BP
- Increased HDL
- No hypoglycemia
- Increased mycotic genital infections
- Small increase in risk for diabetic ketoacidosis

Figure 1: Sodium-glucose cotransporter-2 (SGLT-2) inhibitor action on the kidneys and heart.

Ahmed et al, EHJ 2017
SGLT-2 Inhibitors

- Empagliflozin (EMPA-REG)
- Canagliflozin (CANVAS)
- Dapagliflozin (DECLARE)

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**Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes**

Bernard Zinman, M.D., Christoph Warner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erk Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

- N=7,028
- Median Follow-up 3.1 Years
- Adults with type II DM and known CVD
- Mean age 63.1 years
- Mean Hgb A1C 8.1%
- Primary Outcome: CVD Death, non-fatal MI, non-fatal stroke
**A Primary Outcome**

- **Patients with Event (%)**
  - Placebo: 13, 15, 17, 19, 22, 25, 30, 35, 40, 45
  - Empagliflozin: 12, 14, 16, 18, 21, 24, 29, 34, 39, 44

- **Hazard ratio, 0.86 (95.02% CI, 0.74–0.99)**
- **P=0.04 for superiority**

**No. at Risk**

- **Empagliflozin**
  - 4687, 4580, 4455, 4328, 3851, 2821, 2359, 1534, 370
- **Placebo**
  - 2333, 2256, 2194, 2112, 1875, 1380, 1161, 741, 166

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**B Death from Cardiovascular Causes**

- **Patients with Event (%)**
  - Placebo: 0, 1, 2, 3, 4, 5, 6, 7, 8, 9
  - Empagliflozin: 1, 2, 3, 4, 5, 6, 7, 8, 9

- **Hazard ratio, 0.62 (95% CI, 0.49–0.77)**
- **P<0.001**

**No. at Risk**

- **Empagliflozin**
  - 4687, 4651, 4608, 4556, 4128, 3079, 2617, 1722, 414
- **Placebo**
  - 2333, 2303, 2280, 2243, 2012, 1503, 1281, 825, 177

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American College of Cardiology

EMPA-REG, NEJM 2015
### ASCVD Outcomes

**Heart Failure and CVD Death**

SGLT-2 Meta-analysis, Lancet 2018

### CENTRAL ILLUSTRATION: Sodium-Glucose Co-Transporter-2 Inhibitors in Patients With and Without Cardiovascular Disease

Death
- With prior cardiovascular disease*: 0.56 [0.44, 0.70]
- Without prior cardiovascular disease*: 0.56 [0.50, 0.63]

Heart failure
- With prior cardiovascular disease*: 0.72 [0.63, 0.82]
- Without prior cardiovascular disease*: 0.61 [0.48, 0.78]

Heart failure + Death
- With prior cardiovascular disease*: 0.63 [0.57, 0.70]
- Without prior cardiovascular disease*: 0.56 [0.50, 0.62]

*Diagnosis of AMI, unstable angina, stroke, heart failure, transient ischemic attack, coronary revascularization (CABG or PCI) or occlusive peripheral artery disease prior to index drug initiation

**SGLT2 inhibitor reduces CV death and worsening HF events in HFrEF patients**

DAPA-HF trial, in HFrEF patients (EF ≤40%) both with and without T2DM (n=4744)

**Primary endpoint: worsening of HF events (unplanned HHF or an urgent HF visit requiring intravenous therapy) and CV death**

**Outcomes with dapagliflozin 10 mg once daily on top of standard care**

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>All-cause death</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 24 months</td>
<td>At 24 months</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>1.15</td>
<td>1.05</td>
</tr>
<tr>
<td>(0.68-1.93)</td>
<td>(0.87-1.23)</td>
</tr>
<tr>
<td>P&lt;0.001</td>
<td>P&lt;0.01</td>
</tr>
</tbody>
</table>

**KCCQ At 8 months**

<table>
<thead>
<tr>
<th>Proportion of patients (%)</th>
<th>≥5 point Improvement</th>
<th>≥5 point deterioration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapagliflozin</td>
<td>70%</td>
<td>30%</td>
</tr>
<tr>
<td>Placebo</td>
<td>50%</td>
<td>50%</td>
</tr>
</tbody>
</table>

**Reduction in Hgb A1C**

**Weight Loss**

**Decreased BP**

**Decreased LDL**

**Decreased inflammation**

**GI side effects**

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**Glucagon-like Peptide-1 receptor agonists**

- Reduction in Hgb A1C
- Weight Loss
- Decreased BP
- Decreased LDL
- Decreased inflammation
- GI side effects

**Figure 2** Glucagon-like peptide-1 receptor (GLP-1-R) agonist actions across various organ systems.

Ahmed et al, EHJ 2017
Glucagon-Like Peptide-1 receptor agonists

- Liraglutide (LEADER)
- Semaglutide (SUSTAIN-6)
- Dulaglutide (REWIND)

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

- **N=9,340**
- Median Follow-up 3.8 years
- Individuals with type II DM and CVD or high risk for CVD
- Mean Age 63 years
- Baseline A1C 8.2%
- Primary End-Point: Cardiovascular Death, non-fatal MI, non-fatal stroke
LEADER Trial, NEJM, 2016

Semaglutide – SUSTAIN-6

Marso et al, SUSTAIN-6, NEJM 2018
Semaglutide – SUSTAIN-6

Marso et al, SUSTAIN-6, NEJM 2018

Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes (PIONEER 7): a multicentre, open-label, randomised, phase 3a trial

Prof Thomas R Pieber, MD ◆ Bruce Bode, MD ◆ Ann Mertens, MD ◆ Young Min Cho, MD ◆ Erik Christiansen, MD ◆ Christin L Hertz, MD ◆ et al. Show all authors

RYBELSUS®
semaglutide tablets
Diabetes Recommendation #4

For adults with T2DM and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor (GLP-1R) agonist to improve glycemic control and reduce CVD risk.

HbA1c 6.5% consistent with T2DM

- Dietary counseling regarding key aspects of a heart-healthy diet (Class I)
- At least 150 minutes/week of moderate to vigorous physical activity (Class I)
- Aggressive treatment of other CVD risk factors
- Consideration of metformin as first-line pharmacologic therapy to improve glycemic control and reduce CVD risk (Class IIa)

HbA1c <7.0% after lifestyle therapies and metformin?

- NO
  - Does the patient have other CVD risk factors?
    - NO
      - Further management of diabetes per primary care provider or endocrinology
    - YES
      - Consideration may be given to an SGLT-2 inhibitor or a GLP-1R agonist to improve glycemic control and reduce CVD risk (Class III)
  - YES
    - Reinforce the importance of diet and physical activity and continue current management
68 y/o Male – 6-Month Follow-up

- Initiated empaglifozin 10mg
- Emphasized continued dietary and exercise habit compliance
  - Weight decreased 4lbs
  - A1C 7.2% -> 6.9%
  - Lantus 33 -> 30 units qAM

Sodium-glucose Cotransporter-2 (SGLT2) Inhibitor Considerations
### SGLT2i Agent Selection: Outcomes Considerations

<table>
<thead>
<tr>
<th>FDA Approved</th>
<th>CV Trial Outcomes</th>
<th>FDA CV Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>CANVAS (2017) ↓ MACE ↓ HF hospitalization</td>
<td>• Reduce the risk of MACE in adults with T2DM and established CVD</td>
</tr>
<tr>
<td>(Invokana®)</td>
<td></td>
<td>• Reduce the risk of ESRD, doubling of Scr, cardiovascular death, and hospitalization for heart failure in adults with T2DM and diabetic nephropathy with albuminuria</td>
</tr>
<tr>
<td></td>
<td>DECLARE (2019) ↓ CV Death or Hospitalization for HF</td>
<td></td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>DAPA-HF (HFrEF) (2019) ↓ Hospitalization for HF ↓ CV death ↓ All-cause mortality</td>
<td>• Reduce the risk of hospitalization for heart failure in adults with T2DM and established CVD or multiple CV risk factors</td>
</tr>
<tr>
<td>(Farxiga®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>EMPA-REG (2015) ↓ MACE ↓ CV Death ↓ All-cause mortality ↓ HF hospitalization</td>
<td>• Reduce the risk of cardiovascular death in adult patients with T2DM and established CVD</td>
</tr>
<tr>
<td>(Jardiance®)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### SGLT2i Contraindications

- Serious hypersensitivity reaction to any agent
- Severe renal impairment or HD
SGLT2i Agent Selection: Renal Considerations

**Renal Function Contraindications**

<table>
<thead>
<tr>
<th>SGLT2i Agent</th>
<th>eGFR Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>eGFR &lt; 30</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>eGFR &lt; 45</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>eGFR &lt; 45</td>
</tr>
</tbody>
</table>

**Renal Outcomes**

- **Canagliflozin**
  - ↓Progression of albuminuria
  - ↓≥40% reduction in eGFR, RRT, or renal death
  - ↓ESRD, doubling of the Scr, or death from renal or CV

- **Dapagliflozin**
  - ↓≥40% decrease in eGFR to <60 ml/min/1.73 m², ESRD, or death from renal cause

- **Empagliflozin**
  - Renal outcomes not evaluated

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**SGLT2i Dosing and Titration**

<table>
<thead>
<tr>
<th>SGLT2i Agent</th>
<th>Starting Dose</th>
<th>Titration</th>
<th>Target Dose</th>
<th>Max Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>100 mg daily</td>
<td>HbA1c, BG</td>
<td>100-300 mg</td>
<td>300 mg*</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>5 mg daily</td>
<td>HbA1c, BG</td>
<td>10 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>10 mg daily</td>
<td>HbA1c, BG</td>
<td>10-25 mg</td>
<td>25 mg</td>
</tr>
</tbody>
</table>

* Max dose 100 mg if eGFR 30-60 mL/minute/m²
Considerations with Concomitant Pharmacotherapy

- **Other Oral Anti-DM Meds**
  - Keep metformin
  - ≤ HbA1c target = SWITCH or 50% dose ↓
  - ≥ HbA1c target = ADD

- **Insulin**
  - Increase risk of hypoglycemia
  - Consider up to a 20% empiric dose reduction
  - Monitor close and adjust

- **Diuretics**: dose reduction vs. close monitoring

- **Antihypertensives**
  - ↓ SBP 2-6 mm Hg / DBP 1-2 mm Hg
  - If BP borderline, consider empiric dose reduction
  - Hold anti-HTNs w/o compelling indications

- Drug interactions = canagliflozin

### Drug-Drug Interactions

- UGT Enzyme Inducers (rifampin, phenytoin, phenobarbital, ritonavir) → ↑ canagliflozin dose
- Digoxin → level monitoring

---

Precautions and Adverse Drug Effects

#### Genital Infections

1-6% of patients

- Mycotic vaginitis/ balanitis most common, no ↑ UTI
- Standard hygiene, responsive to topical antifungals
- Perineal necrotizing fasciitis (12 cases over 5 years)

#### Hypoglycemia

- Uncommon
- Higher risk with sulfonylureas or insulin

#### Volume Depletion

26 events/1000 pt years

- Correct hypovolemia before initiating
- Daily weights and BP in first week
- May result in orthostatic hypotension
SGLT2 Inhibitors and Limb Amputation

- Mainly toe and metatarsal
- Observed in RCT for canagliflozin, not others
  - Rare = 6.3 vs. 3.4 amputations per 1,000 patient-years of observation after a median follow-up of 126 weeks
  - Not shown to be dose-dependent
- Risk highest = history of amputation, active foot ulceration, significant neuropathy, PAD
- Standard precautions = regular foot exams and podiatrist evaluation

- Study | Comparator | Events | Results (95% CI)
--- | --- | --- | ---
14 RCTs | Placebo or active AHA | 2.2 (1.8%) versus 3.6 (3.3%) | OR 1.40 (1.31–2.31)
CANVAS | Placebo | 6.3 versus 5.4 per 1,000 pt-yr | HR 1.37 (1.21–2.57)
Phase II-IV RCTs | Placebo or active AHA | 0.5 versus 2.2 per 1,000 pt-yr | RR 0.23 (0.08–0.63)
EMPA-REG OUTCOME | Placebo | 6.8 (1.9%) versus 4.9 (1.8%) | RR 1.30 (0.70–2.40)
14 RCTs | Placebo or active AHA | 4.6 (1.3%) versus 9.4 (1.1%) | RR 1.00 (NS)
30 RCTs | Placebo or active AHA | 6.0 (1.3%) versus 3.7 (0.9%) | RR 1.94 (NS)

US retrospective cohort study | Active AHA | 99 versus 87 (1.0% versus 1.2% per 1,000 pt-yr) | HR 0.90 (0.80–1.04)
US Department of Defense Military Health System | Active AHA | 2.7 versus 0.3 (0.1% per 1,000 pt-yr) | HR 2.60 (1.31–5.12)


SGLT2 Inhibitors and Diabetic Ketoacidosis

- **Mechanism**: rapid ↑ in urinary glucose excretion → ↓ plasma insulin levels + corresponding ↑ glucagon secretion → ↑ gluconeogenesis by the liver + ↑ lipolysis → ketogenesis → ketoacidosis
- Rare = ~1.3 events per 1000 person years
- Often euglycemic/mild hyperglycemic
- Hold in situations that could precipitate DKA
- Hold 3 days before major surgery
- Counsel patients on signs/symptoms of DKA

- **Risk Factors**
  - Rapid, empiric ↓ in insulin dose
  - Unable to eat
  - Persistent N/V/D
  - New low-carb diet
  - Excessive ETOH intake
Monitoring of SGLT2 Inhibitors

- Closer home BG monitoring for first 4 weeks
- Daily weights for the first week
- Daily BP (if possible) for the first week
- Baseline and periodic monitoring of renal function
  - ↓ eGFR ~3 to 4 ml/min/1.73 m² is expected after initiation
- HbA1c at 1-3 months
- Signs and symptoms of ADRs

Glucagon-like peptide (GLP)-1 receptor agonist Considerations
GLP1-RA Agent Selection: Outcomes Considerations

<table>
<thead>
<tr>
<th>FDA Approved</th>
<th>CV Trial Outcomes</th>
<th>FDA CV Indications</th>
<th>Reduced Risk:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albiglutide (Tanzeum®)</td>
<td>HARMONY (2018)</td>
<td>None</td>
<td>MACE</td>
</tr>
<tr>
<td></td>
<td>↓ MACE</td>
<td></td>
<td>MI</td>
</tr>
<tr>
<td>Dulaglutide (Trulicity®)</td>
<td>REWIND (2019)</td>
<td>None</td>
<td>MACE</td>
</tr>
<tr>
<td></td>
<td>↓ MACE</td>
<td></td>
<td>MI</td>
</tr>
<tr>
<td></td>
<td>↓ Stroke</td>
<td></td>
<td>Stroke</td>
</tr>
<tr>
<td>Liraglutide (Victoza®)</td>
<td>LEADER (2016)</td>
<td>Reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ MACE</td>
<td></td>
<td>CV Death</td>
</tr>
<tr>
<td></td>
<td>↓ CV Death</td>
<td></td>
<td>All Cause Mortality</td>
</tr>
<tr>
<td>Semaglutide (Ozempic®, Rybelsus®)</td>
<td>SUSTAIN-6* (2016)</td>
<td>None</td>
<td>MACE</td>
</tr>
<tr>
<td></td>
<td>↓ MACE</td>
<td></td>
<td>Stroke</td>
</tr>
</tbody>
</table>

*designed and powered as a noninferiority trial. Testing for superiority for the primary CV outcome was not prespecified

GLP1-RA Contraindications

- Serious hypersensitivity reaction to any agent
- Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2
- History of pancreatitis?
GLP1-RA Agent Selection: Renal Considerations

**Renal Function Contraindications**

- **Albiglutide**
  - None
  - GI ADEs increase

- **Duliglutide**
  - None
  - No changes in PK

- **Liraglutide**
  - None

- **Semaglutide**
  - None
  - No changes in PK

**Renal Outcomes**

- **Post-marketing case reports of AKI and worsening CKD**

- **Duliglutide**
  - ↓ New macroalbuminuria, a sustained decline in eGFR of ≥30%, or chronic RRT

- **Liraglutide/Semaglutide**
  - ↓ new onset of macroalbuminuria or a doubling of the Scr and an eGFR of ≤45 ml, the need for CRRT, or death from renal disease

---

**GLP1-RA Dosing and Titration**

<table>
<thead>
<tr>
<th>Starting Dose</th>
<th>Titration</th>
<th>Target Dose</th>
<th>Max Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Albiglutide</strong> 30 mg SC Weekly</td>
<td>HbA1c, BG</td>
<td>5 weeks</td>
<td>30-50 mg</td>
</tr>
<tr>
<td><strong>Dulaglutide</strong> 0.75 mg SC Weekly</td>
<td>HbA1c, BG</td>
<td>≥1 week</td>
<td>1.5 mg</td>
</tr>
<tr>
<td><strong>Liraglutide</strong> 0.6 mg SC Daily</td>
<td>HbA1c, BG</td>
<td>≥1 week</td>
<td>1.8 mg</td>
</tr>
<tr>
<td><strong>Semaglutide SC</strong> 0.25 mg SC Weekly</td>
<td>HbA1c, BG</td>
<td>4 weeks</td>
<td>0.5-1 mg</td>
</tr>
<tr>
<td><strong>Semaglutide PO</strong> 3 mg PO daily</td>
<td>HbA1c, BG</td>
<td>30 days</td>
<td>7-14 mg</td>
</tr>
</tbody>
</table>
Considerations with Concomitant Pharmacotherapy

• HbA1c well-controlled/history of hypoglycemic events
  • ↓ sulfonylurea by 50% (glipizide, glyburide, etc.)
  • ↓ basal insulin dose by 20%

• Discontinue DPP-4 inhibitors (“gliptins”)
  • both work through GLP-1 signaling

Drug-Drug Interactions

• None

Precautions and Adverse Drug Effects

**GI Side Effects**
(Fullness, N/V/D)

• Dose dependent and transient but can last weeks
• Caution/avoid with a history of gastroparesis
• Small meals, eat slow, stop before full

**Hypoglycemia**

• Rare
• Typically only occurs with concomitant insulin/sulfonylureas

**Pancreatitis**

• Noted post-marketing, not in RCTs
• Asymptomatic, 20% increases in enzymes common
• Many studies excluded patients with a history
Monitoring of GLP1 Receptor Agonists

- Closer home BG monitoring for first 4 weeks
- HbA1c at 1-3 months
- Signs and symptoms of ADRs
- Guideline-recommended eye examinations before starting therapy if not done within the last 12 months (semaglutide)

Considerations in Selecting Between Classes

<table>
<thead>
<tr>
<th>SGLT2i Favored</th>
<th>GLP1-RA Favored</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFrEF History</td>
<td>Hypotension</td>
</tr>
<tr>
<td>CKD History (eGFR &gt;30)</td>
<td>eGFR &lt;30</td>
</tr>
<tr>
<td>Needle avoidance</td>
<td>Once weekly dosing</td>
</tr>
<tr>
<td>Persistent NVD on GLP1</td>
<td>History of amputation or risk factors</td>
</tr>
<tr>
<td>History of pancreatitis, gastroparesis, thyroid cancer</td>
<td>Recurrent genital infections, DKA on SGLT2</td>
</tr>
</tbody>
</table>