Innovations in GLP-1 Receptor Agonist Therapy: Patient-Centered Strategies to Overcome Barriers and Reduce Cardiometabolic Risk in Type 2 Diabetes Mellitus
Richard E. Pratley, MD
Director
AdventHealth Diabetes Institute
Senior Scientist
Translational Research Institute for Metabolism and Diabetes
Orlando, Florida
Faculty Disclosures

**Consulting Fees**
Astra Zeneca; GlaxoSmithKline; Glytec, LLC; Janssen Pharmaceuticals, Inc.; Ligand Pharmaceuticals, Inc.; Lilly; Merck; Mundipharma; Novo Nordisk Pharmaceuticals; Pfizer; Sanofi US

**Speakers Bureau**
Novo Nordisk Pharmaceuticals

**Contracted Research**
Lexicon Pharmaceuticals; Ligand Pharmaceuticals, Inc.; Lilly; Merck; Novo Nordisk Pharmaceuticals; Sanofi US

*All Honoraria and fees are directed to a non-profit supporting research and education*
What can Mobile Coach do for you?

- Remind you of key content learned in today’s session
- Help set goals for your week and weeks to come
- Challenge you with interactive questions
- Provide practical advice to implement content learned into practice
Sign Up for Mobile Coach!

- Text “Hi Aaron” to (505) 357-1236
- OR fill out the back of the postcard in front of you and return to an Integrity CE representative
- This is not mandatory; You may opt out at any time
Learning Objectives

- Explain geographic trends in access to endocrinologists and define the critical role of PCPs in the management of T2DM
- Compare the underlying pathophysiological mechanisms and pharmacokinetic/pharmacodynamic profiles for currently available and emerging GLP-1 RA agents
- Evaluate updated guideline recommendations and the clinical trial data on the efficacy and safety of specific GLP-1 RAs, in addition to recent CVOT, patient satisfaction, and adherence data
- Identify common provider and patient-related barriers so that GLP-1 RAs can be introduced to more effectively control glucose, improve cardiometabolic risk factors, and increase patient satisfaction and adherence
- Describe the optimal use of GLP-1 RAs in the context of practice-based clinical scenarios
Access to Specialized Diabetes Care in the US

- Many individuals in the US lack access to an endocrinologist.

- Number of individuals in the US with diabetes: **30.3 million**

- Total number of active physicians specializing in endocrinology, diabetes, and/or metabolism in the US: **7,495**

Lu et al. *BMC Health Serv Res.* 2015;15(1):541; Available at: [https://www.aamc.org/download/493090/data/2018‐aamc‐physician‐specialty‐data‐report.pdf](https://www.aamc.org/download/493090/data/2018‐aamc‐physician‐specialty‐data‐report.pdf); Available at: [https://www.cdc.gov/media/releases/2017/p0718‐diabetes‐report.html](https://www.cdc.gov/media/releases/2017/p0718‐diabetes‐report.html)
The Evolving Role of PCPs in T2DM Management

- PCPs deliver clinical care to ~90% of individuals with T2DM
- This will likely increase over time with the growth of the aging population
- T2DM management has become increasingly complex:

  - Minimizing risk for hyper- and hypoglycemia
  - Facilitating lifestyle changes
  - Navigating multiple medication classes (including combination therapies) and medical device options
  - Managing cardiovascular risk
  - Addressing comorbid conditions

Shrivastav et al. *Diabetes Spectr.* 2018;31(3):279-287
CV Risk in T2DM

- T2DM is associated with a two- to threefold greater risk of CV events
- CVD is responsible for ~80% of mortality in T2DM
- Reducing hyperglycemia does not significantly reduce CV risk and mortality
- Insulin resistance is associated with CV risk factors including obesity, dyslipidemia, hypertension, endothelial dysfunction, and procoagulant state (i.e., MetS)
- MetS is a principal factor responsible for increased CV risk in T2DM
- Improvement of CV risk factors reduces CV events and mortality in T2DM
- Molecular mechanisms of insulin resistance are direct, independent contributors to atherosclerosis

Sex Differences in Relative Risk for CHD and Stroke in T2DM

CHD, coronary heart disease

Historically, clinical trials focused on establishing glucose-lowering properties of antidiabetic treatments rather than defining CV impact.

Uncertainty about their potential effects on CV risk led to the 2008 FDA mandate that new antihyperglycemic agents be assessed more thoroughly for CV safety.

Subsequent clinical trials have revealed a significant benefit of several glucose-lowering medications on CV outcomes, including CV and total mortality, without increased risk of hypoglycemia.
CaseScribe Whiteboard Animation: Communicating Effectively to Introduce Patients to GLP-1 RAs
Case Study Discussion

- How would you characterize Susan’s current health status?
- In addition to what we’ve just learned about Susan, what other information is needed in order to help her achieve greater success in managing her health?
- What are the goals of treatment for Susan?
Patient-centered Management in T2DM

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

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

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

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

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

**CONSIDER SPECIFIC FACTORS THAT IMPACT CHOICE OF TREATMENT**
- Individual HbA1c target
- Impact on weight and hypoglycemia
- Side effect profile of medication
- Complexity of regimen, i.e., frequency, mode of administration
- Choose regimen to optimize adherence and persistence
- Access, cost, and availability of medication

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

ASCVD = Atherosclerotic Cardiovascular Disease; CKD = Chronic Kidney Disease; HF = Heart Failure; DSMES = Diabetes Self-Management Education and Support; SMBG = Self-Monitor Blood Glucose.

Davies et al. *Diabetes Care* 2018;42(S1):S1–S194.
Approach to Individualization of Glycemic Targets

### Hypertension:

<table>
<thead>
<tr>
<th>Existing ASCVD or 10-year ASCVD risk &gt;15%</th>
<th>Target BP &lt;130/80 mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-year ASCVD risk &lt;15%</td>
<td>Target BP &lt;140/90 mmHg</td>
</tr>
</tbody>
</table>

### Dyslipidemia:

<table>
<thead>
<tr>
<th>Fasting TG levels ≥500 mg/dL</th>
<th>Evaluate for secondary causes of hypertriglyceridemia and consider medical therapy to reduce pancreatitis risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting or nonfasting TG levels 175–499 mg/dL</td>
<td>Address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that raise triglycerides</td>
</tr>
<tr>
<td>LDL ≥70 mg/dL on maximally tolerated statin dose</td>
<td>Consider adding an additional therapy (e.g., ezetimibe or PCSK9 inhibitor)</td>
</tr>
</tbody>
</table>

AACE/ACE ASCVD Risk Categories

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

Risk Levels:
- **High:** DM but no other major risk and/or age <40
- **Very High:** DM + major ASCVD risk(s) (HTN, Fam Hx, low LDL-C, smoking, CKD3,4)*
- **Extreme:** DM plus established clinical CVD

AACE/ACE Comprehensive Type 2 Diabetes Management Algorithm: Available at: [https://www.aace.com/pdfs/diabetes/AACE_2019_Diabetes_Algorithm_FINAL_ES.pdf](https://www.aace.com/pdfs/diabetes/AACE_2019_Diabetes_Algorithm_FINAL_ES.pdf)
The Majority of Patients with T2D Are Trying to Lose Weight

How do you feel about your weight?

- I am not at all happy with it: 62%
- I am somewhat unhappy with it: 23%
- I am somewhat happy with it: 7%
- I am happy with it: 7%
- No answer: 1%

Are you trying to lose weight?

- Yes: 71%
- No: 29%

2017 T2D in America Survey. Available at: https://type2diabetes.com/living/10-things-you-should-know-about-type-2-diabetes-in-america/8/
Hypoglycemia Is a Significant Obstacle to Achieving Optimal Treatment

Case Study Discussion

- Based on the goals of her treatment, what modifications to Susan’s treatment plan would you make?
- What factors would figure most prominently into your decision-making process?
- What do current guidelines recommend with regard to treatment selection?
<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy</th>
<th>Hypoglycemia</th>
<th>Weight change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>High</td>
<td>No</td>
<td>Neutral (potential for modest loss)</td>
</tr>
<tr>
<td>SGLT-2 inhibitors</td>
<td>Intermediate</td>
<td>No</td>
<td>Loss</td>
</tr>
<tr>
<td>GLP1-RAs</td>
<td>High</td>
<td>No</td>
<td>Loss</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Intermediate</td>
<td>No</td>
<td>Neutral</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>High</td>
<td>Yes</td>
<td>Gain</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>High</td>
<td>Yes</td>
<td>Gain</td>
</tr>
<tr>
<td>Insulin</td>
<td>Higher</td>
<td>Yes</td>
<td>Gain</td>
</tr>
</tbody>
</table>
## Impact of Antihyperglycemic Therapies on CV Outcomes

<table>
<thead>
<tr>
<th></th>
<th>ASCVD</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Potential benefit</td>
<td>Neutral</td>
</tr>
<tr>
<td>SGLT-2 inhibitors</td>
<td>Benefit: EMPA, CANA, DAPA</td>
<td>Benefit: EMPA, CANA</td>
</tr>
<tr>
<td>GLP1-RAs</td>
<td>Benefit: LIRA, SEMA, EXE ER, DULA</td>
<td>Neutral</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Neutral</td>
<td>Potential risk: SAXA, ALO</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Potential benefit: PIO</td>
<td>Increased risk</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>Insulin</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
</tbody>
</table>

*FDA-approved for CVD
EMPA, empagliflozin; CANA, canagliflozin; DAPA, dapagliflozin; LIRA, liraglutide; SEMA, semaglutide; EXE, exenatide; DULA, dulaglutide; LIXI, lixisenatide; SAXA, saxagliptin; ALO, alogliptin; PIO, pioglitazone

Adapted from: Standards of Medical Care in Diabetes - 2020. *Diabetes Care* 2020;43 (Supplement 1): S1-S2.
### SGLT-2 Inhibitors and GLP1-RAs: Specific CV Indications

<table>
<thead>
<tr>
<th></th>
<th>As adjunct to diet and exercise to improve glycemic control in T2DM</th>
<th>To reduce the risk of CV death in T2DM and CVD</th>
<th>To reduce the risk of MACE in T2DM and established CVD or multiple CV risk factors</th>
<th>Hospitalization for HF in T2DM and established CVD or multiple CV risk factors</th>
<th>To reduce the risk for end-stage kidney disease in T2DM and diabetic nephropathy with albuminuria &gt;300 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CANA</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>DAPA</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>LIRA</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEMA</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXE ER</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DULA</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MACE, CV death, nonfatal MI and stroke

*Adapted from: Standards of Medical Care in Diabetes - 2020. Diabetes Care 2020;43 (Supplement 1): S1-S2.*
The EMPA-REG OUTCOME Trial

*Excluding silent MI


Treatment with empagliflozin was associated with a lower rate of cv death, nonfatal MI*, or nonfatal stroke vs placebo.

Hazard ratio, 0.86 (95.02% CI, 0.74–0.99)
P=0.04 for superiority
The LEADER Trial

Treatment with liraglutide was associated with a lower rate of cv death, nonfatal MI, or nonfatal stroke among patients with T2DM

## Impact of SGLT2 Inhibitor Therapy on CV Outcomes

### Hazard Ratio for Primary and Other Trial Outcomes

<table>
<thead>
<tr>
<th>SGLT2i</th>
<th>Composite MACE</th>
<th>CV Death</th>
<th>Non-fatal MI</th>
<th>Non-fatal Stroke</th>
<th>HHF</th>
<th>All-cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EMPA-REG</strong></td>
<td>Empagliflozin</td>
<td>0.86*</td>
<td>0.62*</td>
<td>0.87</td>
<td>1.24</td>
<td>0.65*</td>
</tr>
<tr>
<td><strong>CANVAS</strong></td>
<td>Canagliflozin</td>
<td>0.86*</td>
<td>0.87</td>
<td>0.85</td>
<td>0.90</td>
<td>0.67*</td>
</tr>
<tr>
<td><strong>DECLARE-TIMI 58</strong></td>
<td>Dapagliflozin</td>
<td>0.93</td>
<td>0.98</td>
<td>0.89</td>
<td>1.01</td>
<td>0.73</td>
</tr>
</tbody>
</table>

*Statistically significant

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>GLP-1 RA</th>
<th>Composite MACE</th>
<th>CV Death</th>
<th>Non-fatal MI</th>
<th>Non-fatal Stroke</th>
<th>HHF</th>
<th>All-cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEADER</td>
<td>Liraglutide</td>
<td>0.87*</td>
<td>0.78*</td>
<td>0.88</td>
<td>0.89</td>
<td>0.87</td>
<td>0.85*</td>
</tr>
<tr>
<td>SUSTAIN 6</td>
<td>Semaglutide</td>
<td>0.74*</td>
<td>0.98</td>
<td>0.74</td>
<td>0.61*</td>
<td>1.11</td>
<td>1.05</td>
</tr>
<tr>
<td>REWIND</td>
<td>Dulaglutide</td>
<td>0.88*</td>
<td>0.91</td>
<td>0.96</td>
<td>0.76*</td>
<td>0.93</td>
<td>0.90</td>
</tr>
<tr>
<td>EXSCEL</td>
<td>Exenatide</td>
<td>0.91</td>
<td>0.88</td>
<td>Not reported</td>
<td>Not reported</td>
<td>0.94</td>
<td>0.86</td>
</tr>
</tbody>
</table>

*Statistically significant

## Renal Effects of Antihyperglycemic Therapies

<table>
<thead>
<tr>
<th>Class</th>
<th>DKD Progression</th>
<th>Dosing/use Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Neutral</td>
<td>Contraindicated with eGFR &lt; 30</td>
</tr>
<tr>
<td>SGLT-2 inhibitors</td>
<td>Benefit: CANA*, EMPA</td>
<td>Renal dose adjustment required (CANA, DAPA, EMPA, ERTU)</td>
</tr>
<tr>
<td>GLP1-RAs</td>
<td>Benefit: LIRA, DULA</td>
<td>Renal dose adjustment required (EX, LIXI); caution when initiating or increasing dose due to risk of acute kidney injury</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Neutral</td>
<td>Renal dose adjustment required (SITA, SAXA, ALO); can be use in renal impairment; no dose adjustment required for LINA</td>
</tr>
<tr>
<td>TZDs</td>
<td>Neutral</td>
<td>No dose adjustment required; generally not recommended in renal impairment (potential for fluid retention)</td>
</tr>
<tr>
<td>SUs</td>
<td>Neutral</td>
<td>GLY: not recommended GLIP and GLIM: initiate conservatively to avoid hypoglycemia</td>
</tr>
<tr>
<td>Insulin</td>
<td>Neutral</td>
<td>Lower insulin doses required with a decrease in eGFR; titrate per clinical response</td>
</tr>
</tbody>
</table>

Glucose-lowering Medications in T2DM: ADA Recommendations for Overall Approach

**FIRST-LINE** therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)

**NO**

**INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF**

- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 years with coronary, carotid or lower extremity artery stenosis >50%, or LVH)

**PREFERABLY**

- GLP-1 RA with proven CVD benefit
  - OR
  - SGLT2i with proven CVD benefit

**IF A1C above target**

- Avoid TZD in the setting of HF
  - If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
    - For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit
    - DPP-4i if not GLP-1 RA
    - Basal insulin
    - TZD
    - SU

**ASCVD PREDOMINATES**

- Indicators of high ASCVD risk (age ≥55 years with coronary, carotid or lower extremity artery stenosis >50%, or LVH)

**HF OR CKD PREDOMINATES**

- Particularly HFpEF (LVEF <55%)
- CKD: Specifically eGFR 30-60 mL/min/1.73 m² or UACR >300 mg/g, particularly UACR >300 mg/g

**COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA**

**IF A1C above target**

- GLP1 RA
- SGLT2i OR TZD
- GLP1 RA OR DPP-4i OR TZD
- SGLT2i OR DPP-4i OR GLP-1 RA

**IF A1C above target**

- Continue with addition of other agents as outlined above

**IF A1C 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

**COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS**

**IF A1C above target**

- GLP-1 RA with good efficacy for weight loss
  - Either/ OR
  - SGLT2i

**IF A1C above target**

- GLP-1 RA with good efficacy for weight loss
  - Either/ OR
  - SGLT2i

**IF A1C above target**

- If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimens with lowest risk of weight gain
  - PREFERABLY
  - DPP-4i (if not on GLP-1 RA) based on weight neutrality

**COST IS A MAJOR ISSUE**

- SU
- T2D

**If A1C above target**

- SU
- T2D

**If A1C above target**

- Insulin therapy (basal insulin with lowest acquisition cost)
  - OR
  - Consider DPP-4i or SGLT2i with lowest acquisition cost **ACTIONED**

**Figure 9.1**—Glucose-lowering medication in type 2 diabetes: overall approach. For appropriate context, see Fig. 4.1. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SU, sulfonylurea; T2D, type 2 diabetes mellitus. Adapted from Davies and colleagues (33,34) Standards of Medical Care in Diabetes - 2020. Diabetes Care 2019;43(S1):S1-S212.
INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF†

CONSIDER INDEPENDENTLY OF BASELINE A1C OR INDIVIDUALIZED A1C TARGET

ASCVD PREDOMINATES
- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 years with coronary, carotid or lower extremity artery stenosis >50%, or LVH)

PREFERABLY
- GLP-1 RA with proven CVD benefit¹
- SGLT2i with proven CVD benefit¹

If A1C above target

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit¹
- DPP-4i if not GLP-1 RA
- Basal insulin⁴
- TZD⁵
- SU⁶

HF OR CKD PREDOMINATES
- Particularly HFrEF (LVEF <45%)
- CKD: Specifically eGFR 30-60 mL/min/1.73 m² or UACR >30 mg/g, particularly UACR >300 mg/g

PREFERABLY
- SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate³

If A1C above target

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate² add GLP-1 RA with proven CVD benefit¹

OR

- Avoid TZD in the setting of HF
- Choose agents demonstrating CV safety:
  - For patients on a SGLT2i, consider adding GLP-1 RA with proven CVD benefit¹
  - DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
  - Basal insulin⁴
  - SU⁶

ASCVD PREDOMINATES

If A1C above target

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit¹
- DPP-4i if not GLP-1 RA
- Basal insulin⁴
- TZD⁵
- SU⁶

HF OR CKD PREDOMINATES

If A1C above target

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate² add GLP-1 RA with proven CVD benefit¹

OR

- Avoid TZD in the setting of HF
- Choose agents demonstrating CV safety:
  - For patients on a SGLT2i, consider adding GLP-1 RA with proven CVD benefit¹
  - DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
  - Basal insulin⁴
  - SU⁶

Established ASCVD
- Indicators of high ASCVD risk (age ≥55 years with coronary, carotid or lower extremity artery stenosis >50%, or LVH)

SGLT2i with proven CVD benefit¹

If eGFR adequate²

If A1C above target

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit¹
- DPP-4i if not GLP-1 RA
- Basal insulin⁴
- TZD⁵
- SU⁶

PREFERABLY
- GLP-1 RA with proven CVD benefit¹
- SGLT2i with proven CVD benefit¹

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF†

CONSIDER INDEPENDENTLY OF BASELINE A1C OR INDIVIDUALIZED A1C TARGET

ASCVD PREDOMINATES
- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 years with coronary, carotid or lower extremity artery stenosis >50%, or LVH)

PREFERABLY
- GLP-1 RA with proven CVD benefit¹
- SGLT2i with proven CVD benefit¹

If A1C above target

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit¹
- DPP-4i if not GLP-1 RA
- Basal insulin⁴
- TZD⁵
- SU⁶

HF OR CKD PREDOMINATES
- Particularly HFrEF (LVEF <45%)
- CKD: Specifically eGFR 30-60 mL/min/1.73 m² or UACR >30 mg/g, particularly UACR >300 mg/g

PREFERABLY
- SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate³

If A1C above target

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate² add GLP-1 RA with proven CVD benefit¹

OR

- Avoid TZD in the setting of HF
- Choose agents demonstrating CV safety:
  - For patients on a SGLT2i, consider adding GLP-1 RA with proven CVD benefit¹
  - DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
  - Basal insulin⁴
  - SU⁶
Case Study Discussion

- What are the relative advantages and disadvantages of the two classes of medication recommended for patients like Susan with established ASCVD and/or CKD (ie, GLP-1RAs and SGLT2 inhibitors)?
- How does Susan’s renal insufficiency impact her treatment selection?
- How would treatment selection be different if Susan’s medical history included HF?
A Closer Look at GLP-1 RA Therapies
<table>
<thead>
<tr>
<th>CV Benefits</th>
<th>Renal Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Relaxation of vascular smooth muscle</td>
<td>• Natriuresis</td>
</tr>
<tr>
<td>• Improvement in lipids</td>
<td>• Weight loss</td>
</tr>
<tr>
<td>• Increased myocardial contractility</td>
<td>• Decreased blood pressure</td>
</tr>
<tr>
<td>• Improved angiogenesis</td>
<td>• Improved endothelial function</td>
</tr>
<tr>
<td>• Decreased plaque stability</td>
<td>• Anti-inflammatory effects</td>
</tr>
<tr>
<td>• Decreased apoptosis and extracellular matrix</td>
<td></td>
</tr>
<tr>
<td>remodeling</td>
<td></td>
</tr>
</tbody>
</table>

Chemical Modifications of GLP-1RAs

Note: Grey circles indicate an altered amino acid sequence compared to native GLP-1.

<table>
<thead>
<tr>
<th>GLP-1 RA</th>
<th>Half-life</th>
<th>$T_{\text{max}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide BID$^1$</td>
<td>2.4 hours</td>
<td>2 hours</td>
</tr>
<tr>
<td>Lixisenatide OD$^2$</td>
<td>3 hours</td>
<td>1.0–3.5 hours</td>
</tr>
<tr>
<td>Liraglutide OD$^3$</td>
<td>13 hours</td>
<td>8–12 hours</td>
</tr>
<tr>
<td>Semaglutide OW$^{4,5}$</td>
<td>165–184 hours (6.5–7.5 days)</td>
<td>24–36 hours (1–1.5 days)</td>
</tr>
<tr>
<td>Dulaglutide OW$^6$</td>
<td>90 hours (3.75 days)</td>
<td>24–48 hours (1–2 days)</td>
</tr>
<tr>
<td>Albiglutide OW$^7$</td>
<td>~5 days</td>
<td>3–5 days</td>
</tr>
<tr>
<td>Exenatide OW$^8$</td>
<td>7–14 days</td>
<td>6–7 weeks</td>
</tr>
</tbody>
</table>

BID, twice daily; GLP-1RA, glucagon-like peptide-1 receptor agonist; OD, once daily; OW, once weekly; $T_{\text{max}}$, time to reach maximum concentration.

GLP-1RA Duration Influences FPG, PPG, and A1c

FPG, fasting plasma glucose; PPG, postprandial plasma glucose.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Developer</th>
<th>Stage of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>BI 456906 (dual-acting glucagon/GLP-1 agonist)</td>
<td>Boehringer Ingelheim</td>
<td>Phase I</td>
</tr>
<tr>
<td>CT 868 (dual GLP-1/GIP receptor modulator)</td>
<td>Carmot Therapeutics</td>
<td>Phase I</td>
</tr>
<tr>
<td>HTI-2088 (GLP-1 peptide)</td>
<td>Hengrui Therapeutics</td>
<td>Phase I</td>
</tr>
<tr>
<td>LAI Sema (insulin LAI287/semaglutide)</td>
<td>Novo Nordisk</td>
<td>Phase I</td>
</tr>
<tr>
<td>OG2023SC (NNC0113) (oral GLP-1)</td>
<td>Novo Nordisk</td>
<td>Phase I</td>
</tr>
<tr>
<td>ORMD-0901 (exenatide oral)</td>
<td>Oramed Pharmaceuticals</td>
<td>Phase I</td>
</tr>
<tr>
<td>PF-06882961 (GLP-1R agonist)</td>
<td>Pfizer</td>
<td>Phase I</td>
</tr>
<tr>
<td>MEDI0382 (cotadutide) (GLP-1/glucagon receptor dual agonist)</td>
<td>MedImmune</td>
<td>Phase II</td>
</tr>
<tr>
<td>PB-119 (exenatide pegylated analogue)</td>
<td>PegBio</td>
<td>Phase II</td>
</tr>
<tr>
<td>TTP273 (oral GLP-1R agonist)</td>
<td>vTv Therapeutics</td>
<td>Phase II</td>
</tr>
<tr>
<td>MK-8521 (GLP-1/glucagon receptor co-agonist)</td>
<td>Merck</td>
<td>Phase II completed</td>
</tr>
<tr>
<td>Efpeglenatide (long-acting GLP-1 agonist)</td>
<td>Sanofi</td>
<td>Phase III</td>
</tr>
<tr>
<td>Tirzepatide (GIP/GLP-1 dual receptor agonist)</td>
<td>Eli Lilly</td>
<td>Phase III</td>
</tr>
<tr>
<td>ITCA 650 (exenatide implant)</td>
<td>Intarcia Therapeutics</td>
<td>Application submitted</td>
</tr>
<tr>
<td>Semaglutide oral (GLP-1 receptor agonist)</td>
<td>Novo Nordisk</td>
<td>Approved September 2019</td>
</tr>
</tbody>
</table>
Discussion

- How do the new and emerging GLP-1RAs compare with those that were previously available?
- What is the anticipated impact of these new therapeutic options? (ie, on weight gain, hypoglycemia, CVD risk, and injection-related barriers)
Efficacy of Oral Semaglutide vs Subcutaneously Injected Liraglutide: Changes in HbA$_{1c}$

PIONEER 4

Mean baseline HbA$_{1c}$: 8.0% (SD 0.7; 64 mmol/mol [SD 8])

Efficacy of Oral Semaglutide vs Subcutaneously Injected Liraglutide: Changes in Body Weight

PIONEER 4

Mean baseline body weight: 94.0 kg (SD 21.0)

Change in Body Weight (kg)

Time Since Randomisation (weeks)

Oral semaglutide
Subcutaneous liraglutide
Placebo

Efficacy of ITCA 650

Kjemset et al. *Diabetes*. 2018, 67(S1)1103-P.
Overcoming Common Treatment Barriers: Focus on GLP-1RAs
If Susan is determined to be a suitable candidate for treatment with a GLP1-RA, how would you go about initiating therapy? What should the first steps be?

What would you do in order to maximize the probability of Susan’s success in using this new therapy?
Barriers to Effective T2DM Treatment

**Patient-based**
- Adverse events (weight gain, hypoglycemia)
- Treatment characteristics (regimen complexity and convenience, dose frequency, injection)
- Education
- Income
- Level of insurance

**Clinician-based**
- Lack of comfort with complexity of injectable therapies
- Lack of comfort with complex patient profiles

**Externally-based**
- Access to healthcare
- Treatment cost
- Insurance requirements (prior authorization, step therapy contingency, non-medical switching)

Consensus Recommendations for the Use of Empowering Language

- Is neutral, nonjudgmental, and based on facts, actions, or physiology/biology
- Is free from stigma
- Is strength based, respectful, and inclusive and that imparts hope
- Fosters collaboration between patients and providers
- Is person-centered (eg, “person with diabetes” is preferred over “diabetic”)

Diabetes Self-management Education

### Diabetes Self-management Education and Support for Adults With Type 2 Diabetes: Algorithm of Care

ADA Standards of Medical Care in Diabetes recommends all patients be assessed and referred for:

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At diagnosis</strong></td>
<td></td>
<td><strong>Annual assessment of education, nutrition, and emotional needs</strong></td>
<td><strong>When new complicating factors influence self-management</strong></td>
<td><strong>When transitions in care occur</strong></td>
</tr>
</tbody>
</table>

When primary care provider or specialist should consider referral:

- **Nutrition**
  - Registered dietitian for medical nutrition therapy

- **Education**
  - Diabetes self-management education and support

- **Emotional Health**
  - Mental health professional, if needed

**Four critical times to assess, provide, and adjust diabetes self-management education and support**

1. **At diagnosis**
   - Newly diagnosed. All newly diagnosed individuals with type 2 diabetes should receive DSME/S
   - Ensure that both nutrition and emotional health are appropriately addressed in education or make separate referrals

2. **Annual assessment of education, nutrition, and emotional needs**
   - Needs review of knowledge, skills, and behaviors
   - Long-standing diabetes with limited prior education
   - Change in medication, activity, or nutritional intake
   - HbA1c out of target
   - Maintain positive health outcomes
   - Unexplained hypoglycemia or hyperglycemia
   - Planning pregnancy or pregnant
   - For support to attain and sustain behavior change(s)
   - Weight or other nutrition concerns
   - New life situations and competing demands

3. **When new complicating factors influence self-management**
   - Change in:
     - Health conditions such as renal disease and stroke, need for steroid or complicated medication regimen
     - Physical limitations such as visual impairment, dexterity issues, movement restrictions
     - Emotional factors such as anxiety and clinical depression
     - Basic living needs such as access to food, financial limitations

4. **When transitions in care occur**
   - Change in:
     - Living situation such as inpatient or outpatient rehabilitation or now living alone
     - Medical care team
     - Insurance coverage that results in treatment change
     - Age-related changes affecting cognition, self-care, etc.

GI-related AEs Across GLP-1 RAs

Patient-reported Reasons for Discontinuation of GLP-1RA Therapy

- Made me feel sick: 64.4%
- Made me throw up: 45.4%
- Prefer oral medication over injections: 39.7%
- Inadequate blood glucose control: 34.5%
- Caused diarrhea/gas/bloating: 26.3%
- Did not help to lose weight: 25.3%
- Injections were painful: 20.1%
- Regular injections too inconvenient: 20.1%
- Injections were too costly: 12.9%
- Concerned about needle size: 11.3%
- Itch/rash/other reactions at injection site: 10.3%
- Difficult to plan daily activities around: 9.8%
- Symptoms of low blood sugar: 9.8%
- Caused weight gain: 7.7%
- Difficult to plan meals around: 4.6%
Management of Adverse GI Effects

- Inform patients initiating GLP-1 RA therapy that GI-related adverse effects may occur initially but are typically transient and mild-to-moderate

- To reduce nausea, advise patients do the following:
  - Consume smaller meals
  - Avoid large or high-fat meals

- Return patient to a lower GLP-1 RA dose for $\geq 1$ week before repeating the incremental dosing steps

CaseScribe Whiteboard Animation: Improving Patient Satisfaction and Addressing Cardiometabolic Risk with GLP-1 RAs
Case Study Discussion

- What do you think is preventing Susan from achieving greater success with her treatment?
- Susan’s case highlights the importance of ensuring that patients are adherent to their prescribed treatment. What strategies would you recommend for improving her adherence?
Key Factors that Influence Medication Adherence

- Perceived treatment efficacy
- Hypoglycemia
- Treatment complexity and convenience
- Cost of treatment
- Medication beliefs
- Physician trust

## Comparative Features of Available GLP1-RAs

<table>
<thead>
<tr>
<th>Agent</th>
<th>Administration frequency</th>
<th>Delivery</th>
<th>Reconstitution required?</th>
<th>Need to attach needle to pen?</th>
<th>Need to prime pen?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dulaglutide (Trulicity)</td>
<td>Once weekly</td>
<td>Single-dose prefilled pens (0.75 mg, 1.5 mg)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Exenatide (Bydureon)</td>
<td>Once weekly</td>
<td>Single-dose dual-chamber pen containing powder (2 mg) and solvent for prolonged-release suspension and single-dose prefilled pen for prolonged-release suspension (2 mg)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Semaglutide (Ozempic)</td>
<td>Once weekly</td>
<td>Multidose prefilled pens (0.25 mg or 0.5 mg/dose, 1 mg/dose)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Semaglutide (Rybelsus)</td>
<td>Once weekly</td>
<td>Orally administered</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Liraglutide (Victoza)</td>
<td>Once daily</td>
<td>Multidose prefilled pen (delivers 0.6, 1.2, or 1.8 mg/dose)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Lixisenatide (Lyxumia)</td>
<td>Once daily</td>
<td>Multidose prefilled pens (10 µg/dose, 20 µg/dose)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Exenatide (Byetta)</td>
<td>Twice daily</td>
<td>Multidose prefilled pens (5 µg/dose, 10 µg/dose)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Real-world Adherence and Persistence with GLP-1RA Therapy

In addition to the things that we’ve just talked about, we should also address Susan’s comment about medication cost. What can we do to help make sure that patients have access to optimal treatment in the face of economic constraints?
Overcoming Cost Barriers: Discount Programs and Databases

Benefits Check Up: www.benefitscheckup.org
Blink Health: www.blinkhealth.com/
FamilyWize: https://familywize.org/
GoodRx: www.goodrx.com/
Inside Rx: www.insiderx.com/
Needy Meds: www.needymeds.org
Partnership for Prescription Assistance: www.pparx.org/
Rx Assist: www.rxassist.org
Rx Hope: www.rxhope.com
SingleCare: www.singlecare.com
Overcoming Cost Barriers: Additional Patient Resources

- **Local Community Health Clinics and Pharmacies**
  - Typically free to patients or require a very small fee
  - Tools for locating a clinic:
    - [https://findahealthcenter.hrsa.gov/](https://findahealthcenter.hrsa.gov/)
    - [http://www.nafcclinics.org/find-clinic](http://www.nafcclinics.org/find-clinic)

- **Patient Assistance Programs**
  - Most pharmaceutical companies offer financial assistance programs to patients having difficulty affording medications and supplies
  - Each program has specific eligibility criteria
Along with maintaining glycemic control, the reduction of risk for poor cardiovascular outcomes is central to the optimal care of patients with T2DM.

Two classes of antidiabetic therapies, the GLP-1RAs and SGLT2 inhibitors, have been shown to significantly improve cardiovascular outcomes in patients with T2DM across numerous large-scale clinical trials.

Among the currently available and emerging GLP-1RAs, individual agents vary with regard to pharmacokinetic and pharmacodynamic profiles and, as a result, may be more or less suitable for a given patient.

Optimal T2DM management requires a patient-centered approach to treatment selection that takes into account individual physiological and behavioral characteristics in order to improve medication adherence, patient satisfaction, and therapeutic outcomes.
Q & A
Thank You!
Connect!

Email:
Richard.Pratley.MD@adventhealth.com

Websites:
www.tri-md.com
www.adventhealthdiabetes.com

@RpratleyMD
@FH_TRI_MD

Richard Pratley