A GUIDELINE APPROACH TO TREATMENT INTENSIFICATION FOR TYPE 2 DIABETES MELLITUS

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Financial Disclosure and Resolution

Under guidelines established under the Standards for Integrity and Independence in Accredited Continuing Education, disclosure must be made regarding relevant financial relationships with ineligible companies within the last 24 months.

I have no relevant financial relationships with ineligible companies to disclose.
Professional Practice Gap

Recent advances in the treatment of diabetes mellitus have led to a drastic change in the guideline driven treatment recommendations. These recommendations have moved from a purely glycemic control method to a treatment that must account for multiple patient characteristics and preferences. There is a significant gap in knowledge on how and when to intensify patient hyperglycemic medications.

Learning Objectives

At the completion of this activity, pharmacists will be able to:

1. Recognize the significance of individualizing glycemic targets and antihyperglycemic medications based on patient characteristics and preferences
2. Apply an intensive insulin therapy treatment plan based on current guidelines
3. Demonstrate how to intensify antihyperglycemic therapy
Presentation Overview

• Medication selection for a patient with diabetes and a history of ASCVD, HF, or CKD
• Medication selection for a patient with diabetes an compelling need to minimize hypoglycemia, minimize weight gain or promote weight loss or if cost is an issue
• Steps to intensify antihyperglycemic agents to injectable as diabetes progresses

Case: Sheldon

• Sheldon’s wife is a technician in the pharmacy. She was complaining to you that her husband didn’t have a primary care provider (PCP).
• It was noted that he was currently on Metformin 500mg po daily for 6 months due to infrequent provider visits.
Case: Sheldon

DISCUSSION

• The pharmacy clinical team in conjunction with the Special Diabetes Program for Indians (SDPI) created the pharmacy-based Intensive Diabetes Management Service (IDMS) to more rapidly and effectively intensify diabetic patients medications.

Case: Sheldon

Goals:

• Intensify diabetic medications more rapidly.
• Be a bridge for diabetic patients waiting on a PCP.
• No more than 6-12 month consult to clinic.
Figure 9.1
Glucose lowering medication in type 2 diabetes: overall approach

Consider Independently of Baseline A1C or Individualized A1C Target
If No Indicators of High-Risk or Established ASCVD, CKD, or HF

**Step 1**: Does the patient have Established ASCVD, CKD, or HF or do they have indicators for?
- ≥55 years with coronary, carotid or lower extremity artery stenosis >50%, or LVH
- LVEF <45%
- DKD and albuminuria

If the answer is “No”

First-Line therapy is metformin and comprehensive lifestyle (including weight management and physical activity)

If +ASCVD/Indicators of High Risk Predominate:

- GLP1 receptor agonist (GLP-1 RA) with proven cardiovascular benefit
  - Liraglutide
  - Semaglutide
  - Dulaglutide
- SGLT2 inhibitor (SGLT2i) with proven cardiovascular benefit
  - Empagliflozin
  - Canagliflozin
  - Dapagliflozin

## CV Outcome Trial Data GLP-1 Receptor Agonists

<table>
<thead>
<tr>
<th>Trial</th>
<th>REWIND(^1)</th>
<th>LEADER(^2)</th>
<th>SUSTAIN-6(^3)</th>
<th>PIONEER(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent</td>
<td>Dulaglutide</td>
<td>Liraglutide</td>
<td>SQ Semaglutide</td>
<td>Oral Semaglutide</td>
</tr>
<tr>
<td>Sample Size</td>
<td>9,901</td>
<td>9,340</td>
<td>3,297</td>
<td>3,183</td>
</tr>
<tr>
<td>Proportion with CVD at baseline</td>
<td>31%</td>
<td>81%</td>
<td>83%</td>
<td>85%</td>
</tr>
<tr>
<td>Median follow-up Years</td>
<td>5.4</td>
<td>3.8</td>
<td>2.1</td>
<td>1.3</td>
</tr>
<tr>
<td>RRR for composite MACE outcome*</td>
<td>12%</td>
<td>13%</td>
<td>26%</td>
<td>21%</td>
</tr>
</tbody>
</table>

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**RRR:** Relative Risk Reduction, *Composite Outcome: Major adverse cardiovascular event (MACE) include CV death, nonfatal myocardial infarction, non-fatal stroke.

At this time only Dulaglutide indicated for Primary and Secondary Patients.\(^5\)

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## SGLT2i Cardiovascular Outcome Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>EMPA-RET OUTCOME(^2)</th>
<th>CANVAS(^3)</th>
<th>DECLARE-TIMI 58(^4)</th>
<th>VERTIS-CV(^5)</th>
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<tbody>
<tr>
<td>Agent</td>
<td>Empagliflozin</td>
<td>Canagliflozin</td>
<td>Dapagliflozin</td>
<td>Ertugliflozin</td>
</tr>
<tr>
<td>Sample Size</td>
<td>7,020</td>
<td>10,142</td>
<td>17,160</td>
<td>8,246</td>
</tr>
<tr>
<td>Proportion with CVD at baseline</td>
<td>100%</td>
<td>65.6%</td>
<td>40.6%</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Median Follow-up (Yrs)</td>
<td>3.1</td>
<td>2.4</td>
<td>4.2</td>
<td>3.5</td>
</tr>
<tr>
<td>RRR for composite MACE outcomes</td>
<td>14%</td>
<td>14%</td>
<td>7%</td>
<td>Not Significant</td>
</tr>
</tbody>
</table>

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If HF Predominates:

Approved Medication for T2D in HF:

- Empagliflozin
- Canagliflozin
- Dapagliflozin

- FDA-approved for HF benefit
  - Dapagliflozin and empagliflozin have primary and secondary benefit to reduce HF
  - Canagliflozin has secondary benefit to reduce HF
  - Avoid pioglitazone, saxagliptin, and alogliptin in HF.

Heart Failure Outcome Trial Data for SGLT2 Inhibitors

<table>
<thead>
<tr>
<th>Trial</th>
<th>Empa-Reg Outcome</th>
<th>Canva2</th>
<th>Credence3</th>
<th>Declare-TIMI 58</th>
<th>Veris-CV4</th>
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</thead>
<tbody>
<tr>
<td>Agent</td>
<td>Empagliflozin</td>
<td>Canagliflozin</td>
<td>Canagliflozin</td>
<td>Dapagliflozin</td>
<td>Ertugliflozin</td>
</tr>
<tr>
<td>Sample size</td>
<td>7,020</td>
<td>10,142</td>
<td>4,401</td>
<td>17,160</td>
<td>8,246</td>
</tr>
<tr>
<td>Proportion with CVD at baseline</td>
<td>&gt;99%</td>
<td>60%</td>
<td>50%</td>
<td>41%</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Median follow-up (years)</td>
<td>3.1</td>
<td>3.6</td>
<td>2.6</td>
<td>4.2</td>
<td>3.5</td>
</tr>
<tr>
<td>RRR for hospitalization for heart failure</td>
<td>34%</td>
<td>33%</td>
<td>39%</td>
<td>27%</td>
<td>30%</td>
</tr>
</tbody>
</table>

If CKD predominates:

- Canagliflozin
- Dapagliflozin
- Empagliflozin

- Benefit seen in COVT’s
- FDA-approved for CKD indication - canagliflozin and dapagliflozin
- Empagliflozin primary renal trial is ongoing

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SGLT2i Renal Outcomes Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>CREDENCE</th>
<th>DAPA-CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent</td>
<td>Canagliflozin</td>
<td>Dapagliflozin</td>
</tr>
<tr>
<td>Renal Outcomes*</td>
<td>4,401</td>
<td>4,304</td>
</tr>
<tr>
<td>Median years follow-up (yrs)</td>
<td>4.6</td>
<td>2.4</td>
</tr>
<tr>
<td>RRR for composite renal outcomes</td>
<td>34%</td>
<td>36%</td>
</tr>
</tbody>
</table>

*renal-specific composite of end-stage kidney disease, a doubling of the creatinine level, or death from renal causes

Treatment/Prevention of CKD: Glucose/A1C control

Recommendations:
• 11.2 Optimize glucose control to reduce the risk or slow the progression of CKD. A
• 11.3a For patient with T2D and diabetic kidney disease (DKD), consider use of a SGLT2i in patients with an eGFR ≥30ml/min/1.73m2 and urinary albumin >300mg/g creatinine. A
• 11.3b In patient with T2D and DKD, consider use of SGLT2i additionally for cardiovascular reduction when eGFR and urinary albumin creatinine are ≥30ml/min/1.73m2 or >300mg/g. A
• 11.3c In patients with CKD who are at increased risk for cardiovascular events, use of a GLP-1 RA reduces renal end point, primarily albuminuria, progression of albuminuria, and cardiovascular events. A


Case Study: Mary

Mary is a 51-year-old Native American Woman with T2D. She wants to lose weight.

Medical History:
• T2D x 4 years
• Hyperlipidemia
• Hypertension
• ASCVD
• Weight Gain of 7lbs in the last 4 months
Case Study: Mary

Medications:
- Metformin ER 2000mg daily

Physical Exam:
- BP: 125/72
- Heart Rate: 74 bpm
- Weight 170 lbs
- Height 5’5”
- BMI: 28.3 kg/m²

Relevant Labs:
- A1C: 7.2%
- Cholesterol: 175 mg/dl
- Triglycerides: 210 mg/dl
- HDL: 45 mg/dl
- LDL: 78 mg/dl
- GFR: >60 ml/min/1.73 m²
- UACR: 18 mg/g

Poll Question #1

What would be the next best second line medication for Mary?

A. Sitagliptin 100mg by mouth daily
B. Pioglitazone 15mg by mouth daily
C. Semaglutide 0.5mg SQ once weekly
D. Glimepiride 4mg by mouth daily
If No Indicators of High-Risk or Established ASCVD, CKD, or HF

**Step 1:** Does the patient have Established ASCVD, CKD, or HF or do they have indicators for?

- ≥55 years with coronary, carotid or lower extremity artery stenosis >50%, or LVH
- LVEF <45%
- DKD and albuminuria

If the answer is “No”

First-Line therapy is metformin and comprehensive lifestyle (including weight management and physical activity)

Indicators for High-Risk or Established ASCVD, CKD, or HF

**NO**

**YES**

Figure 9.1 Glucose lowering medication in type 2 diabetes; overall approach

Need to minimize hypoglycemia

- SU and insulin cause most hypoglycemia.
- Consider Glimepiride or Glipizide XL.
- Consider U100, U300 Glargine, and Insulin Degludec.

Need to Minimize Weight Gain or Promote Weight Loss

- Weight loss: Semaglutide > Liraglutide > Dulaglutide > Exenatide > Lixisenatide
  - Average weight loss: 1.8 to 4.1kg
- Weight Neutral to loss: Metformin, SGLT2I, DDP4I
- Weight Gain: SU, TZD, and Insulin
Cost is a Major Issue

- If no specific Comorbidities (i.e., no established cardiovascular disease (CVD), low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities).

Table 9.2 – Median Monthly Cost of maximum approved daily dose of noninsulin glucose-lowering agents in the U.S.

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Rising Cost of Medication

- Dramatic rise in cost over the previous decade
- Significant portion of this cost is passed to patients and families
- Major source of stress for patients which leads to worse outcomes
- Important to have an open conversation with patients

2021 American Diabetes Association Guidelines

- 9.11 Recommendation for treatment intensification for patients not meeting treatment goals should not be delayed. A
- The medication regimen and medication-taking behavior should be reevaluated at regular intervals (every 3–6 months) and adjusted as needed to incorporate specific factors that impact choice of treatment. E
Case Study: Johnny

Johnny is a 43 year old Native American man who recently divorced and is living on his own. He is currently in between jobs and lost his health insurance. He also is very fearful of injection.

Past Medical History:
- T2D for 4 years
- No history of ASCVD, HF, CKD
- Has been more active recently and trying to eat out less.

Medications:
- Sitagliptin 100mg daily
- Metformin 1000mg twice daily

Physical Exam:
- BP:127/70mmHg
- HR: 72 bpm
- Wt: 145 lbs
- Ht: 5’11”
- BMI: 20.2 kg/m²

Relevant Labs:
- A1C: 6.6%
- Cholesterol: 145mg/dl
- TG: 156mg/dl
- HDL: 40mg/dl
- LDL: 87mg/dl
- GFR: >60ml/min/1.73m²
- UACR: <30mg/g
Poll Question #2

What would be the best treatment plan for Johnny?

A. No change in his medications
B. Stop sitagliptin and start oral semaglutide 7mg daily with metformin
C. Stop sitagliptin and start empagliflozin 10mg daily with metformin
D. Stop sitagliptin and start glimepiride 4mg daily with metformin

In Caring for T2D, **Timing** is Important

- **Physiology and Psychology**
  - Glycemic burden
  - Loss of beta cell function
  - Risk of complications
    - Microvascular (renal, retinal, neural)
- **Physiology and Approach**
  - Act with urgency
  - Act aggressively
  - Address risk of CVD
  - Address risk of CKD
  - Screen for retinopathy, neuropathy
  - Understanding: This is a progressive disease
  - Expectation: Need to advance disease
What Injectable Should I Use First?

- 9.10 In patients with T2D, a GLP-1 RA is preferred to insulin when possible. A

- The early introduction of insulin should be considered if there is evidence of catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels > 10% or blood glucose levels ($\geq$ 300mg/dl) are very high. E
Scientific Rationale for Combining a GLP-1 RA with Basal Insulin

- **GLP-1 RA**
  - Simple to initiate
  - Pronounced postprandial glucose control
  - Reduced risk of hypoglycemia
  - Weight reduction
  - Achieve A1C targets in 40-60%

- **Basal Insulin Analogs**
  - Simple to initiate
  - Control nocturnal and FPG
  - Lower hypoglycemia risk vs. NPH
  - Modest weight gain (1-3 kg)
  - Achieve A1C target in 40%

Initiation of Basal Insulin

- Add basal analog or bedtime NPH insulin

Start 10 units a day or 0.1-0.2 units/kg daily

Choice of basal insulin should be based on patient-specific factors, including cost.

**Titration of Basal Insulin**

**START**
Basal Insulin
Daily dose: 10 units or 0.1-0.2 units/kg
Set Individualized FPG target

**ADJUST**
Choose evidence-based titration algorithm (e.g., increase 2 units every 3 days) to reach FPG target without hypoglycemia

Continue regimen and check A1C every 3 months/biannual

For hypoglycemia determine cause, if no clear cause, lower dose 10-20%

Assess Adequacy of Basal Insulin Dose

- Consider clinical signals to evaluate overbasalization
  - Basal dose > 0.5 units/kg
  - Elevated bedtime-morning and/or post-prandial differential
  - Hypoglycemia (aware or unaware)
  - High variability

Intensifying to Prandial Therapy

If Above A1C target

Add Prandial Insulin
Usually one dose with the largest meal or meal with greatest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate

**INITIATION:**
- 4 IU a day or 10% of basal insulin dose
- If A1C <8% consider lowering the basal dose by 4 IU a day or 10% of basal dose

**TITRATION:**
- Increase dose by 1-2 IU or 10-15% twice weekly
- For Hypoglycemia determine cause, if no clear reason lower dose by 10-20%

If on bedtime NPH, consider converting to twice-daily NPH regimen
Conversion based on individual needs and current glycemic control. The following is a possible approach:

**INITIATION:**
- Total Dose: 80% of current bedtime NPH dose
- 2/3 given in the morning
- 1/3 given at bedtime

**TITRATION:**
- Twice based on individualized needs

If A1C above target

Stepwise additional injections of prandial insulin (i.e., two, then three additional injections)

Consider self-mixed/split insulin regimen
Can adjust NPH and short/rapid-acting insulins separately

INITIATION:
- Total NPH dose = 80% of current NPH dose
- 2/3 given before breakfast
- 1/3 given before dinner
- Add 4 IU of short/rapid-acting insulin to each injection or 10% of reduced NPH dose

TITRATION:
- Titrate each component of the regimen based on individualized needs

Proceed to full basal bolus regimen (i.e., basal insulin and prandial insulin with each meal)

Consider twice daily premix insulin regimen

INITIATION:
- Usually unit per unit at the same total insulin dose, but may require adjustment to individual needs

TITRATION:
- Titrate based on individualized needs


Self-mixed/Split Insulin Regimen

- Can adjust NPH and short/rapid-acting insulins separately

- Initiation
  - Total NPH dose = 80% of current NPH dose
  - 2/3 given before breakfast and 1/3 before dinner
  - Add 4 IU of short/rapid-acting insulin to each injectable or 10% of reduced NPH dose

- Titration:
  - Titrate each component of the regimen based on individualized needs

Considering Oral Therapy in Combination with Injectable Therapies

**SGLT2i**
- If on SGLT2i continue treatment
- Consider adding SGLT2i
  - Established CVD
  - A1C above target or as weight reduction aid

**Beware**
- Diabetic Ketoacidosis (euglycemic)
- Instruct on sick-day rules
- Do not down-titrate insulin over-aggressively

**METFORMIN**
- Continue treatment if possible

**DPP-4i**
- Stop DPP-4i if GLP-1 initiated

**Sulfonylurea (SU)**
- Stop SU when initiating insulin OR reduce dose
- Consider stopping SU if prandial insulin initiated or on a premix regimen

**TZD**
- Stop TZD when initiating insulin OR reduce dose

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**Case Study: Ed**

Ed is a 66 year old Hispanic man who has been resistant to insulin therapy in the past. After several discussions with his provider, diabetes educator, and family he is now open to using insulin.

**Past Medical History:**
- T2D for 15 years
- Hyperlipidemia
- Hypertension
- PVD
- CKD
Case Study: Ed

**Medications:**
- Canagliflozin 100mg daily
- Metformin 500mg twice daily
- Glimepiride 4mg daily
- Dulaglutide 1.5mg weekly

**Relevant Labs:**
- A1C: 9.1%
- Cholesterol: 145mg/dl
- TG: 180mg/dl
- HDL: 42mg/dl
- LDL: 65mg/dl
- GFR: 42ml/min/1.73m²
- UACR: <342mg/g

**Physical Exam:**
- BP: 129/82mmHg
- HR: 62 bpm
- Wt: 181 lbs
- Ht: 5'6"
- BMI: 29.2 kg/m²

Poll Question #3

If Ed’s individualized A1C target is less than 8% what would be the next best treatment decision?

A. Start basal insulin 10 units injected at bedtime
B. Increase glimepiride to 8mg daily
C. Increase metformin to 2000mg/day
D. Increase canagliflozin to 300mg daily
Follow up to Case Study: Ed

- Ed started glargine U300 at 10 units SQ at bedtime and it was titrated using the 3-0-3 method until his fasting glucose was steadily below 130mg/dl.
- Current basal dose is 30 units
- Follow up A1C is 8.1 and fasting glucoses average around 100 mg/dl.

Poll Question #4

What would be the next best step for Ed to improve glycemic control?

A. Increase glimepiride to 8mg/day
B. Increase metformin to 2000mg/day
C. Add prandial insulin 4 units SQ TID AC
D. Add prandial insulin 4 units SQ prior to largest meal of the day
Diabetic Trials to Note

- The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) is a long-term study of different treatments for type 2 diabetes
- SOUL - Semaglutide cardiovascular outcomes trial in patients with type 2 diabetes
- Empagliflozin in Heart Failure with a Preserved Ejection Fraction (EMPEROR-PRESERVED HF)

Conclusion

- Medications should be selected based on patient characteristics including the presence of ASCVD, CKD, HF, and the need to avoid hypoglycemia, to promote weight loss, or cost issues.
- Intensifying injectables should not be delayed if not to A1C goal.
- GLP-1 RA is the first preferred injectable unless signs of catabolism exist or blood glucose is extremely high (>10% or glucose >300mg/dl).
- If A1C not to goal, avoid overbasalization and intensify in a step-wise approach.
Clinical Pearls

• Consider adding a GLP-1 RA or SGLT2i regardless of glycemic status if patient has ASCVD, CKD, or HF.

• Proven benefit in CVD, CKD, or HF means it has a label indication for one these. In the ADA algorithm be sure to read the fine print!

• REMEMBER: Once your reach 0.5 units/kg with basal insulin dose the dose response curve flattens and weight gain and hypoglycemia become more possible. Once you reach this level consider a GLP-1 RA or bolus insulin dose starting with largest meal of the day.

Changes in your Practice

What changes do you intend to make in your practice as a result of this activity?
Additional Resources

- American Diabetes Association 2021 Standards of Medical Care in Diabetes
- https://diatribe.org
- https://www.diabeteseducator.org

References

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