How to Use the American Diabetes Association’s Type 2 Diabetes Algorithm

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Disclosures of Interest

• I have no conflicts
Key points to emphasize

New information -- Updated October 5, 2018 at EASD meeting in Berlin

1. Update informed by evidence generated in the past 2 years

2. Greater focus on lifestyle interventions, with increased emphasis on weight loss and obesity management, including metabolic surgery

3. Greater focus on patient related issues and self-management which have a major impact on success of any pharmacological interventions

4. Preferred choices of glucose-lowering agents driven by new evidence from CVOT and consideration of areas of major clinical need (for example weight and risk of hypoglycemia)

5. GLP-1 RAs are preferred to insulin as first injectable

Balancing Risks and Benefits for Personalized Goals

**More Stringent Control**
- No hypoglycemia
- Less complexity/polypharmacy
- Lifestyle or metformin only
- Short disease duration
- Long life expectancy
- No CVD

**Less Stringent Control**
- History of severe hypoglycemia
- High burden of therapy
- Longer disease duration
- Limited life expectancy
- Extensive co-morbidity
- CVD
Improving Glycemic Management

• Focus on treatments for glycemic control
  • Behavioral approaches
  • Medications
  • Metabolic surgery

• Address increasing complexity of patient centered therapeutic decisions in the context of expanding therapeutic options and new information on benefits and risks

Putting the Patient at the Center of Care
Shared decision making in type 2 diabetes

SDM can improve
  • decision quality
  • patient knowledge
  • patient risk perception

Ethical imperative for support of patients’ autonomy
Diabetes Self-Management Education and Support (DSMES)

- Is available to patients at critical times
- Individualized to the needs of the person, including language and culture
- Structured theory-driven written curriculum with supporting materials
- Delivered in group or individual settings by trained educators
- Promote healthy eating, physical activity, good medication-taking behavior, and increase self-efficacy
- Supports person and their family in developing attitudes, beliefs, knowledge and skills to self-manage diabetes
- Includes core content and monitoring of patient progress, including health status, quality of life.
- Evidence-based

Empathic patient-centered care

- Patients with diabetes often live with multiple chronic conditions
- Providers & health care systems should prioritize the delivery of empathic, individualized patient-centered care
- To determine what is the best management option for each patient, consider each individual's
  - personal, social and biomedical context,
  - his/her values,
  - reasons he/she values the available options, and
  - relative contribution of each option in terms of benefits, harms, costs and inconveniences.
Persistence and medication adherence

• Mean medication adherence rate ≈ 75%, average proportion of patients adherent to medication < 70%.

• Adherence slightly varies between orals vs injectable therapy and individual classes

• Discontinuation rates range from 10% to 60% (both in observational studies and in clinical trials)

Clinical Inertia

Clinical inertia: failure of healthcare providers to initiate or intensify therapy when indicated, due to:

• overestimation of care provided

• use of “soft” reasons to avoid intensification of therapy

• lack of education, training, and practice organization aimed at achieving therapeutic goals
Glucose-Lowering Medication in Type 2 diabetes: overall approach

**Foundational therapy is metformin and comprehensive lifestyle management (including weight management and physical activity)**

**Metformin** is the preferred initial glucose lowering medication for most people with T2D.

This recommendation is based on the efficacy, safety, tolerability, and extensive clinical experience with this medication. Results from UKPDS showed benefits of initial treatment with metformin in clinical outcomes related to diabetes, with less hypoglycemia and weight gain than with insulin or sulfonylureas.

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*American Diabetes Association.*

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![UKPDS 35: any 1% decrease in HbA1c was associated with risk reduction (p<0.05 for all)](image)

*American Diabetes Association.*

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*British Medical Journal 2000; 321: 405-412*
Metformin Monotherapy

1. Recommended dosage 1000 mg BID (if tolerated)
2. Titrate slowly over 1-2 weeks (500 mg increments and always with food)
3. Use of extended release **highly recommended**
4. Continue full dosing if GFR > 45 cc/min
5. Reduce to 500 mg BID if GFR 30-45 cc/min
6. STOP Metformin if GFR less than 30
**Recommendation:**
The stepwise addition of glucose lowering medication is generally preferred to initial combination therapy.

While there is some support for initial combination therapy due to the greater initial reduction of A1C than metformin alone, there is little evidence that this approach is superior to sequential addition of medications for maintaining glycemic control, or slowing the progression of diabetes.

Since the absolute efficacy of most oral medications rarely exceeds 1% reduction in A1C, initial combination therapy should be considered in patients presenting with A1C levels more than 1.5% above their target. Fixed-dose formulations can improve medication-taking behavior when combination therapy is used and may achieve glycemic targets more rapidly.

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**American Diabetes Association.**
Recommended Process for Glucose Lowering Medication Selection: Where Does New Evidence From Cardiovascular Outcome Trials Fit In?

DECISION CYCLE FOR PATIENT-CENTRED GLYCAEMIC MANAGEMENT IN TYPE 2 DIABETES

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 socio-economic context

American Diabetes Association.
Foundational therapy is metformin and comprehensive lifestyle management (including weight management and physical activity)

Step 1: Assess cardiovascular disease
Presence of cardiovascular disease is compelling indication
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes  

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes  

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes  

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes  

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes  

Considerations

- ASCVD is defined differently across trials
  - Established CVD (e.g. MI, stroke, revascularization procedure)
  - Very high cardiovascular risk
- Each cardiovascular outcomes trial, while large, is a single experiment
- It is not always clear whether differences in trial findings within a drug class are related to trial design or to true differences in the individual medications
  - Where evidence suggests a hierarchy, this is noted
CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ASCVD OR CKD

Liraglutide and CVOT

NEJM 375: 311, 2016
Semaglutide and CVOT

Semaglutide and HbA1c/Weight
### GLP-1 and CVOT

<table>
<thead>
<tr>
<th></th>
<th>Lixisenatide</th>
<th>Liraglutide</th>
<th>Semaglutide</th>
<th>Exenatide</th>
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<tbody>
<tr>
<td>3 pt MACE</td>
<td>1.02</td>
<td>0.87</td>
<td>0.74</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>0.89-1.17</td>
<td>0.78-0.97</td>
<td>0.58-0.95</td>
<td>0.83-1.00</td>
</tr>
<tr>
<td>CV Death</td>
<td>0.98</td>
<td>0.78</td>
<td>0.98</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>0.78-1.22</td>
<td>0.66-0.93</td>
<td>0.65-1.48</td>
<td>0.76-1.02</td>
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<tr>
<td>Non-fatal MI</td>
<td>1.03</td>
<td>0.88</td>
<td>0.74</td>
<td>0.97</td>
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<tr>
<td></td>
<td>0.87-1.22</td>
<td>0.75-1.03</td>
<td>0.51-1.08</td>
<td>0.85-1.10</td>
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<tr>
<td>Non-fatal stroke</td>
<td>1.12</td>
<td>0.89</td>
<td>0.61</td>
<td>0.85</td>
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<tr>
<td></td>
<td>0.79-1.58</td>
<td>0.72-1.11</td>
<td>0.38-0.99</td>
<td>0.70-1.03</td>
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<tr>
<td>HF Hospitalization</td>
<td>0.96</td>
<td>0.87</td>
<td>1.11</td>
<td>0.94</td>
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<tr>
<td></td>
<td>0.75-1.23</td>
<td>0.73-1.05</td>
<td>0.77-1.61</td>
<td>0.78-1.13</td>
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<tr>
<td>All cause mortality</td>
<td>0.94</td>
<td>0.85</td>
<td>1.05</td>
<td>0.86</td>
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<tr>
<td></td>
<td>0.78-1.13</td>
<td>0.74-0.97</td>
<td>0.74-1.50</td>
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### SGLT2i and MACE

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>Placebo</td>
<td>Treatment</td>
<td>Placebo</td>
<td></td>
<td></td>
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<tr>
<td><strong>Patients with atherosclerotic cardiovascular disease</strong></td>
<td>EMPA-REG OUTCOME</td>
<td>4687</td>
<td>3333</td>
<td>772</td>
<td>37.4</td>
<td>43.9</td>
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<tr>
<td></td>
<td>CANVAS Program</td>
<td>3756</td>
<td>2900</td>
<td>796</td>
<td>34.1</td>
<td>41.3</td>
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<tr>
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<td>DECLARE-TIMI 58</td>
<td>3474</td>
<td>3500</td>
<td>1020</td>
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<td>41.0</td>
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<tr>
<td>Fixed effects model for atherosclerotic cardiovascular disease (p=0.0002)</td>
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<td></td>
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<tr>
<td><strong>Patients with multiple risk factors</strong></td>
<td>CANVAS Program</td>
<td>2039</td>
<td>1447</td>
<td>215</td>
<td>15.8</td>
<td>15.5</td>
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<tr>
<td></td>
<td>DECLARE-TIMI 58</td>
<td>5108</td>
<td>5078</td>
<td>539</td>
<td>13.4</td>
<td>13.3</td>
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<td>Fixed effects model for multiple risk factors (p=0.98)</td>
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<td></td>
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</tr>
</tbody>
</table>
If ASCVD Predominates:

GLP-1 RA with proven cardiovascular benefit
- Strongest evidence for liraglutide > semaglutide > exenatide LAR

SGLT2-i with proven cardiovascular benefit
- Modest evidence for empagliflozin > canagliflozin

Caveats and Questions

No evidence of CVD benefit in those at lower cardiovascular risk
The combination of SGLT2-i and GLP-1 RA has not been tested in cardiovascular outcome trials
CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED HF OR CKD

Among patients with ASCVD in whom HF coexists or is of concern, SGLT2 inhibitor are recommended

**Rationale:** Patients with T2D are at increased risk for heart failure with reduced or preserved ejection fraction

Significant, consistent reductions in hospitalization for heart failure have been seen in SGLT2-i trials

**Caveat:** trials were not designed to adjudicate heart failure

Majority of patients did not have clinical heart failure at baseline
## SGLT2i and Heart Failure

### Patients with atherosclerotic cardiovascular disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment (n)</th>
<th>Placebo (n)</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>4687</td>
<td>2333</td>
<td>461</td>
<td>19.7</td>
<td>30.1</td>
<td>0.66 (0.55-0.79)</td>
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<tr>
<td>CANVAS Program</td>
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<td>2900</td>
<td>524</td>
<td>21.0</td>
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<td>0.77 (0.65-0.92)</td>
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<tr>
<td>DECLARE-TIMI 58</td>
<td>3474</td>
<td>3500</td>
<td>597</td>
<td>19.9</td>
<td>23.9</td>
<td>0.83 (0.71-0.98)</td>
</tr>
</tbody>
</table>

Fixed effects model for atherosclerotic cardiovascular disease (p<0.0001)

### Patients with multiple risk factors

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment (n)</th>
<th>Placebo (n)</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
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</thead>
<tbody>
<tr>
<td>CANVAS Program</td>
<td>2039</td>
<td>1447</td>
<td>128</td>
<td>8.9</td>
<td>9.8</td>
<td>0.83 (0.79-1.19)</td>
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<td>5078</td>
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<td>7.0</td>
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<td>0.84 (0.79-1.04)</td>
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</tbody>
</table>

Fixed effects model for multiple risk factors (p=0.0634)

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### American Diabetes Association.

Lancet 393:31, 2019

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## SGLT2i and Heart Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment (n)</th>
<th>Placebo (n)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>462</td>
<td>244</td>
<td>114</td>
<td>63.6</td>
<td>85.5</td>
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<tr>
<td>CANVAS Program</td>
<td>803</td>
<td>658</td>
<td>201</td>
<td>35.4</td>
<td>56.8</td>
<td>0.61 (0.46-0.80)</td>
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<tr>
<td>DECLARE-TIMI 58</td>
<td>852</td>
<td>872</td>
<td>314</td>
<td>45.1</td>
<td>55.5</td>
<td>0.79 (0.63-0.99)</td>
</tr>
</tbody>
</table>

Fixed effects model for history of heart failure (p<0.0001)

### Patients with no history of heart failure

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment (n)</th>
<th>Placebo (n)</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>4295</td>
<td>2689</td>
<td>339</td>
<td>15.5</td>
<td>24.9</td>
<td>0.63 (0.51-0.78)</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>4932</td>
<td>3689</td>
<td>449</td>
<td>13.6</td>
<td>15.2</td>
<td>0.67 (0.72-1.06)</td>
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<tr>
<td>DECLARE-TIMI 58</td>
<td>7730</td>
<td>7706</td>
<td>599</td>
<td>8.9</td>
<td>10.5</td>
<td>0.84 (0.72-0.99)</td>
</tr>
</tbody>
</table>

Fixed effects model for no history of heart failure (p<0.0001)

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### American Diabetes Association.

Lancet 393:31, 2019
SGLT2i and Renal Progression

**Recommendation:**

For patients with type 2 diabetes and chronic kidney disease, consider use of a sodium–glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist shown to reduce risk of chronic kidney disease progression, cardiovascular events, or both. C

Several of these medications have demonstrated renal benefit and cardiovascular benefit and should be considered as part of treatment.
CHOosing GLucose-LowerIng meDICation IF COMPELLING NEED TO MINIsmise HYPOglycemia

In those without established ASCVD OR CKD

Use principles in Figure 1

First-line therapy is metformin
If HbA1c ≥ 7.7 mmol/mol (58 %) above individualised HbA1c target consider early combination therapy

<table>
<thead>
<tr>
<th>If HbA1c above target</th>
<th>DPP-4i</th>
<th>GLP-1 RA</th>
<th>SGLT2i if eGFR adequate</th>
<th>T2D6</th>
</tr>
</thead>
<tbody>
<tr>
<td>If HbA1c above target</td>
<td>If HbA1c above target</td>
<td>SGLT2i or T2D6</td>
<td>GLP-1 RA or DPP-4i or T2D6</td>
<td>SGLT2i or DPP-4i or GLP-1 RA</td>
</tr>
<tr>
<td>If HbA1c above target</td>
<td>If HbA1c above target</td>
<td>If HbA1c above target</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continue with addition of other agents as outlined above

If HbA1c above target

Consider the addition of sulfonylurea OR basal insulin
- Choose later generation SUs with lower risk of hypoglycemia
- Consider basal insulin with lower risk of hypoglycemia

American Diabetes Association.

CHOosing GLucose-LowerIng meDICation IF COMPELLING NEED TO MINIsmise WeIGHT GAIN OR PROMOTE WeIGHT LOSS

In those without established ASCVD OR CKD

Use principles in Figure 1

First-line therapy is metformin
If HbA1c ≥ 7.7 mmol/mol (58 %) above individualised HbA1c target consider early combination therapy

<table>
<thead>
<tr>
<th>If HbA1c above target</th>
<th>GLP-1 RA with good efficacy for weight loss1</th>
<th>SGLT2i if eGFR adequate1</th>
</tr>
</thead>
<tbody>
<tr>
<td>If HbA1c above target</td>
<td>If HbA1c above target</td>
<td></td>
</tr>
</tbody>
</table>

Implement strategies for maximising weight loss

<table>
<thead>
<tr>
<th>General lifestyle advice</th>
<th>Medical nutritional therapy</th>
<th>Exercise patterns</th>
<th>Physical activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider medication for weight loss</td>
<td>Non-surgical energy restriction for weight loss</td>
<td>Weight loss of 1kg can lead to remission of T2DM in patient ≤ 5 years’ duration, consider evidence-based weight loss programmes</td>
<td></td>
</tr>
<tr>
<td>Consider metabolic surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Sulfonylurea + biguanide + thiazolidinediones + glinide is preferred.
2. Addition of metformin to individual agent with respect to individualised target of HbA1c is calculated and maintained.
3. Choose later generation SUs with lower risk of hypoglycemia.
4. Use of metformin is better tolerated through lower risk for GI effects.

American Diabetes Association.
**Consensus Recommendation:** In patients who need the greater glucose-lowering effect of an injectable medication, GLP-1 receptor agonists are the preferred choice to insulin. For patients with extreme and symptomatic hyperglycaemia, insulin is recommended.
Case Study

- **Patient:** Ms. F
- **Age:** 57
- **Occupation:** CEO of local non-for-profit
- **Diabetes Hx:** 6 years; BMI 27; no cx; struggles with weight, eats out frequently, daily schedule
- **Current Meds:** metformin, saxagliptin, insulin detemir 36 units HS
- **A1C:** 8.1%, anti-GAD negative, eGFR >60 ml/min/1.73m
- **BG pattern:** fasting average 142 mg/dL, post-meal average 207 mg/dL, no hypoglycemia
- **Patient/Provider Goals:** avoid complications, facilitate weight loss, dosing simplicity
Strategy for Ms F

- Ensure she has received (adequate) DSMES
- Maximize metformin (if not already)
- Consider GLP-1 as next step
- D/C DPP4i if add GLP-1
- Taper insulin if possible. Consider switch to longer acting insulin or give detemir BID if insulin still needed and insurance dictates choice

Case Study

- **Patient:** Mrs. L
- **Age:** 77
- **Occupation:** retired teacher
- **Diabetes Hx:** 12 years, no retinopathy, no nephropathy, no neuropathy sx, SU caused hypoglycemia, SGLT2-i yeast infections, pioglitazone edema
- **Cardiovascular History:** none
- **Current Diabetes Meds:** metformin 500mg BID, pioglitazone 30 mg daily
- **A1C:** 8.3%
- **BG pattern:** fasting average 145 mg/dL, post-meal average 200 mg/dL, infrequent hypoglycemia
- **Patient/Provider Goals:** healthy aging
Strategy for Mrs L

- Establish HbA1c goal
- Ensure she has received (adequate) DSMES
- Maximize metformin
- D/C pioglitazone
- Consider DPP4i

Case Study

- **Patient:** Mr. K
- **Age:** 51
- **Occupation:** drives a delivery truck
- **Diabetes Hx:** 8 years, BMI 28; microalbumin/creatinine ratio < 20; + non-proliferative retinopathy, active, eats out every day
- **A1c:** A1C: 9.5%, anti-GAD negative, eGFR >60 ml/min/1.73m²
- **Cardiovascular History:** CVA last year (slurred speech, left-sided weakness) w/ full recovery, stopped smoking
- **Current Diabetes Meds:** metformin 500 mg ER 3 tabs per day, pioglitazone 30 mg daily
- **Cardiovascular Meds:** ARB, statin, ASA
- **BG pattern:** fasting average 160-180 mg/dL, post-meal average 260 mg/dL, no hypoglycemia
- **Patient/Provider Goals:** avoid complications, support healthy eating
Strategy for Mr K

- Establish HbA1c goal
- Encourage lifestyle changes and DSMES
- Maximize metformin
- D/C pioglitazone
- Consider GLP-1 vs basal insulin
- If HbA1c not at goal with changes, consider addition of basal insulin to GLP-1
Recommendations

In most patients who need the greater glucose-lowering effect of an injectable medication, glucagon-like peptide 1 receptor agonists are preferred to insulin. B

Intensification of treatment for patients with type 2 diabetes not meeting treatment goals should not be delayed. B

The medication regimen should be reevaluated at regular intervals (every 3–6 months) and adjusted as needed to incorporate new patient factors. E

Conclusions

An important early step in this new approach: consider the presence or absence of ASCVD, CKD, and heart failure.

In patients with ASCVD, some GLP-1 RA and SGLT2-i are recommended in these patients.
Conclusions

Among patients with atherosclerotic cardiovascular disease at high risk of heart failure or in whom heart failure coexists, sodium–glucose cotransporter 2 inhibitors are preferred.

For patients with type 2 diabetes and chronic kidney disease, consider use of a sodium–glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist shown to reduce risk of chronic kidney disease progression, cardiovascular events, or both.

• Studies of HF or CKD as primary outcome are ongoing with SGLT2-i.

Summary

Consider the presence or absence of ASCVD, CKD and HF
Start with metformin if tolerated, then:

- In patients with ASCVD a GLP-1 RA or SGLT2-i is recommended
- In patients with HF SGLT2-i is recommended
- In patients with CKD, with or without ASCVD consider an SGLT2-i
  Agents with proven benefit are preferred
  ASCVD, CKD and HF affects choice of additional glucose lowering medication
Thank you