Smart Use of Meds for Our Diabetic Patients

Elizabeth Seaquist MD
Director, Division of Endocrinology and Diabetes
Vice Chair for Clinical Affairs
Department of Medicine
Pennock Family Chair in Diabetes Research
University of Minnesota
Presenter Disclosure

Have served as consultant to Sanofi, Novo Nordisk, Lilly, and Zucera and obtained research support from Lily

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63 year old man with 5 years of type 2 diabetes. Had a MI last year. Currently takes metformin 2000 mg/day, has stable weight, and exercises by walking 150 min per week. BMI 33. BP 112/70. A1c 8.2

Which of the following medications would you add to his regimen to improve glycemic control?

A. Glipizide
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D. Sitagliptin
Melissa

40 year old woman with 9 years of type 2 diabetes. She has no other medical problems. Currently takes metformin 2000 mg/day, exercises at a fitness center 3 times a week.

BMI 27.8. BP 120/66. HgbA1c 8.2

Which of the following medications would you add to his regimen to improve glycemic control?

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Management of Hyperglycemia in Type 2 Diabetes 2018—A Consensus Report by the ADA and EASD

• Evidence based consensus report presented a EASD in Oct 2017
• In print in Diabetes Care, Diabetologia November 2018
• Greater focus on lifestyle interventions, with increased emphasis on weight loss and obesity management, including metabolic surgery
• Greater focus on patient related issues and self-management which have a major impact on success of any pharmacological interventions
DEcision Cycle for Patient-Centred Glycaemic Management in Type 2 Diabetes

**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)

**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

**Ongoing Monitoring and Support Including:**
- Emotional well-being
- Check tolerability of medication
- Monitor glycaemic status
- Biofeedback including SMBG, weight, step count, HbA1c, BP, lipids

**Goals of Care**
- Prevent complications
- Optimise quality of life

**Consider Specific Factors Which Impact Choice of Treatment**
- Individualised HbA1c target
- Impact on weight and hypoglycaemia
- Side effect profile of medication
- Complexity of regimen i.e. frequency, mode of administration
- Choose regimen to optimise 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

**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

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Foundational therapy is metformin and comprehensive lifestyle management (including weight management and physical activity)
Consider important comorbidities that should influence the choice of a particular glucose-lowering medication

Among patients with type 2 diabetes with established atherosclerotic cardiovascular disease (ASCVD), sodium-glucose cotransporter 2 (SGLT2) inhibitors or glucagon-like peptide 1 (GLP-1) receptor agonists with proven cardiovascular benefit are recommended as part of glycemic management.
CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ASCVD OR CKD

**ASCVD PREDOMINATES**

- **EITHER/ OR**
  - GLP-1 RA with proven CVD benefit\(^1\)
  - SGLT2i with proven CVD benefit\(^1\), if eGFR adequate\(^2\)

**If HbA\(_{1c}\) 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:
- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin\(^4\)
- TZD\(^5\)
- SU\(^6\)

**HF OR CKD PREDOMINATES**

- **PREFERABLY**
  - SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate\(^3\)

**OR**

- If SGLT2i not tolerated or contraindicated or if eGFR less than adequate\(^2\)
  - Add GLP-1 RA with proven CVD benefit\(^1\)

**If HbA\(_{1c}\) above target**

- Avoid TZD in the setting of HF
- Choose agents demonstrating CV safety:
  - Consider adding the other class with proven CVD benefit\(^1\)
  - DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
  - Basal insulin\(^4\)
  - SU\(^6\)
If ASCVD Predominates:

GLP-1 receptor agonist with proven cardiovascular benefit
- Liraglutide > semaglutide > exenatide LAR

SGLT2 inhibitor with proven cardiovascular benefit
- 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

**HF OR CKD PREDOMINATES**

- PREFERABLY
  - SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate
  - OR
  - If SGLT2i not tolerated or contraindicated or if eGFR less than adequate
    - add GLP-1 RA with proven CVD benefit

- If HbA$_1c$ above target
  - Avoid TZD in the setting of HF
  - Choose agents demonstrating CV safety:
    - Consider adding the other class with proven CVD benefit
    - DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
    - Basal insulin
    - SU

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1. Proven CVD benefit means it has labeled indication of reducing CVD events. For GLP-1 RA, strong evidence of licagliflozin + empagliflozin = metformin. For SGLT2i evidence modestly stronger for empagliflozin vs canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to labeled indication of eGFR < 60 (initiation and continued use)
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Dipeptidyl peptidase-4 inhibitors have demonstrated CV safety
5. Low dose may be better tolerated through less well studied for CV effects
6. Choose later-generation SU with lower risk of hypoglycemia
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 inhibitor trials

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

Majority of patients did not have clinical heart failure at baseline
Consensus Recommendation:

For patients with type 2 diabetes and CKD, with or without cardiovascular disease, consider the use of an SGLT2 inhibitor shown to reduce CKD progression or, if contraindicated or not preferred, a GLP-1 receptor agonist shown to reduce CKD progression.

Several of these medications have demonstrated renal benefit and cardiovascular benefit and should be considered as part of treatment.
CKD Considerations

For SGLT2-i adequate eGFR differs between countries and compounds

SGLT2-i are registered as glucose-lowering agents to be started if eGFR>45-60 ml/min/1.73m² and stopped at eGFR 45-60, as glucose-lowering effect declines with eGFR

SGLT2-i CVOTs included patients with eGFR>30, and there were no excess adverse events in subjects with eGFR<60

For GLP-1 RA gastrointestinal side effects increase with declining renal function

GLP-1 RA are not recommended in end stage renal disease due to limited experience
Consensus Recommendation

Metabolic surgery is a recommended treatment option for adults with type 2 diabetes and

(1) a BMI ≥ 40 kg/m$^2$ (BMI ≥ 37.5 kg/m$^2$ in people of Asian ancestry) or

(2) a BMI 35.0-39.9 (32.5-37.4 in people of Asian ancestry) who do not achieve durable weight loss and improvement in comorbidities with reasonable non-surgical methods
GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)

IF HbA1c ABOVE TARGET PROCEED AS BELOW

ESTABLISHED ASCVD OR CKD

NO

WITHOUT ESTABLISHED ASCVD OR CKD

ASCVD PREDOMINATES

HF OR CKD PREDOMINATES

PREFERABLY SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs

IF SGLT2i not tolerated or contraindicated or if eGFR less than adequate1 and GLP-1 RA with proven CVD benefit

COMPELLING NEED TO MINIMISE HYPOGLYCAEMIA

COMPELLING NEED TO MINIMISE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

COST IS A MAJOR ISSUE™

1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence of liraglutide > semaglutide > exenatide. For SGLT2i evidence moderate stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary in terms of individual agent with regard to indicated level of GFR for initiation and continued use.
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs.
4. Dapagliflozin or ipragliflozin have demonstrated CVD safety.
5. Low dose may be better in terms of glucose though less well studied by CV outcomes.
6. Choose Late generation SU with lower risk of hypoglycaemia.
7. Empagliflozin (Jardiance) + pioglitazone (Actos) = intense - HbA1c.
8. Sensible in hyperglycaemia: diuretic = losartan = ramipril = bisoprolol.
9. If specific contraindication (i.e., no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related complications).
10. Consider country- and region-specific cost of drugs. In some countries SGLT2i relatively more expensive and DPP-4i relatively cheaper.

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American Diabetes Association.
CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPPELLING NEED TO MINIMISE HYPOGLYCAEMIA

In those without established ASCVD OR CKD

Use principles in Figure 1

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY 3-6 MONTHS

Identify patient groups at highest risk of hypoglycaemia and set and/or adjust HbA₁c target to minimise risk of hypoglycaemia

First-line therapy is metformin

If HbA₁c is ≥ 17 mmol/mol (1.5%) above individualised HbA₁c target consider early combination therapy

If HbA₁c above target

DPP-4i

GLP-1 RA

SGLT2i if eGFR adequate

TZD

If HbA₁c above target

If HbA₁c above target

SGLT2i or TZD

SGLT2i or TZD

GLP-1 RA or DPP-4i or TZD

SGLT2i or DPP-4i or GLP-1 RA

If HbA₁c above target

Continue with addition of other agents as outlined above

If HbA₁c above target

Consider the addition of sulfonylurea OR basal insulin:
- Choose later generation SU with lower risk of hypoglycaemia
- Consider basal insulin with lower risk of hypoglycaemia

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1. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
2. Low dose TZDs are better tolerated
3. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMISE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

In those without established ASCVD OR CKD

Use principles in Figure 1

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (7-12 MONTHS)

First-line therapy is metformin
If HbA1c is ≥ 17 mmol/mol (1.5%) above individualised HbA1c target consider early combination therapy

If HbA1c above target

GLP-1 RA with good efficacy for weight loss

EITHER/ OR

SGLT2i if eGFR adequate

If HbA1c above target

SGLT2i if eGFR adequate

GLP-1 RA with good efficacy for weight loss

If HbA1c above target

If triple therapy required or SGLT2i and/or GLP-1 RA not tolerated or contraindicated use regimen with lowest risk of weight gain

PREFERABLY

DPP-4i (if not on GLP-1 RA) based on weight neutrality

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:
- SU
- TZD
- Basal insulin

Implement strategies for maximising weight loss

General lifestyle advice
- Medical nutritional therapy
- Eating patterns
- Physical activity

Non-surgical energy restriction for weight loss
Weight loss of 15kg can lead to remission of T2DM in patient
- 6 years’ duration, consider evidence-based weight loss programmes

Consider medication for weight loss

Consider metabolic surgery

1. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Choose later generation SU with lower risk of hypoglycaemia
4. Low dose may be better tolerated though less well studied for CVD effects

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CHOOSING GLUCOSE-LOWERING MEDICATION IF COST IS A MAJOR ISSUE

In those without established ASCVD OR CKD

Consider additional DSMES to support weight loss/maintenance and avoidance of hypoglycaemia

Use principles in Figure 1

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3-4 MONTHS)

First-line therapy is metformin
If HbA1c is ≥ 17 mmol/mol (1.5%) above individualised HbA1c target consider early combination therapy

If HbA1c above target

SU
TZD

If HbA1c above target

TZD
SU

If HbA1c above target

Insulin therapy: Basal insulin with lowest acquisition cost OR
Consider DPP-4i or SGLT2i with lowest acquisition cost

1. Choose later-generation SU to minimise risk of hypoglycaemia
2. Consider country- and region-specific cost of drugs. In some countries, TZD relatively more expensive and DPP-4i relatively cheaper
3. Low-dose TZDs are better tolerated
**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 reasons or better A1c and weight outcomes in clinical trials.** For patients with extreme and symptomatic hyperglycemia, insulin is recommended.
Overall Summary

The management of hyperglycemia in type 2 diabetes has become complex with the number of glucose-lowering medications now available. Patient-centered decision-making and support and consistent efforts at improving diet and exercise remain the foundation of all glycemic management.

Initial use of metformin, followed by addition of glucose-lowering medications based on patient co-morbidities and concerns is recommended as we await answers to the many questions that remain.
Which basal insulin should you use?

• SWITCH 1 and SWITCH 2 showed patients had less hypoglycemia when they received randomized treatment with degludec vs. glargine (both published in JAMA 2017)

• DEVOTE study demonstrated that T2DM subjects randomized to degludec had less hypoglycemia, mortality, and CVD events than subjects randomized to glargine (NEJM 2017)

• BRIGHT trial randomized T2DM subjects to degludec vs. U300 glargine. Essentially no difference in risk of hypoglycemia (Diabetes Care 2018)
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