Guideline-based approaches to reducing cardiovascular risk in diabetes

Introduction

In this CPD-accredited report, guidance from a number of international and South African expert societies is evaluated to determine best practice when looking after type 2 diabetic patients, with a focus on cardiovascular protection in primary care. The recently released American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the primary prevention of cardiovascular disease are useful, as they are as clear and concise as possible. These guidelines also reflect the concern that cardiovascular disease is still a leading cause of death in diabetes, with 65% of deaths due to coronary heart disease, heart failure and stroke.¹

• Late-breaking news – 2019 ESC guidelines on diabetes and cardiovascular disease from the 2019 ESC Congress, Paris²

• The main recommendation is that GLP-1 RAs and SGLT-2 inhibitors be used as first-line treatment in type 2 diabetes patients with established disease or at high risk of cardiovascular disease. High risk in this ESC guidance is defined as patients with diabetes mellitus duration >10 years without target organ damage but with any other additional risk factor (hypertension, dyslipidaemia or inflammation)³

• Liraglutide is specifically recommended in patients with type 2 diabetes and cardiovascular disease or at very high cardiovascular risk to reduce the risk of death and to reduce cardiovascular events.

ACC/AHA provides a simple pathway

The first two principles of lifestyle change and team-based care have been visualised with further priority actions in an easy-to-use clinical tool (Figure 1).¹ The consensus pathway in type 2 diabetes is simple: if a patient has (a) type 2 diabetes and (b) established clinical atherosclerotic cardiovascular disease, the clinician should address two things concurrently. Firstly, a ‘guideline-directed medical therapy’ is required – essentially metformin, lifestyle changes, antiplatelet therapies, blood pressure-lowering and lipid-lowering. Concurrently, the clinician should consider adding a sodium-glucose co-transporter-2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor agonist (GLP-1 RA) with demonstrated cardiovascular outcomes benefit (Figure 2).¹
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Figure 1. Primary prevention: Lifestyle changes therapy and team-based care clinical tool

- **Diet**: Emphasis on intake of vegetables, fruits, nuts, legumes, fish and whole grains.
- **Tobacco**: Pharmacotherapy + behavior interventions recommended to maximize quit rates.
- **Cholesterol**: Assess ASCVD Risk, personalize with risk enhancers, reclassify with CAC as needed.
- **High Blood Pressure**: Maintain blood pressure below 130/80 mm Hg.
- **Physical Activity**: Perform ≥150 mins/week of moderate or ≥75 mins/week of vigorous physical activity.
- **Aspirin Use**: Low-dose aspirin for primary prevention now reserved for select high-risk patients.

**Type II Diabetes**
- Control through diet and exercise.
- Metformin (primary therapy), SGLT-2 inhibitor or GLP-1 receptor agonist (secondary).

**HbA1c >6.5% consistent with T2DM**

- **YES**
  - Dietary counselling regarding key aspects of a heart-healthy diet (Class I).

- **NO**
  - At least 150 minutes/week of moderate to vigorous physical activity (Class I).

- **NO**
  - Aggressive treatment of other CVD risk factors.

- **YES**
  - Consideration of metformin as first-line pharmacologic therapy to improve glycemic control and reduce CVD risk (Class IIa).

**HbA1c >7.0% after lifestyle therapies and metformin?**

- **YES**
  - Consideration may be given to an SGLT-2 inhibitor or a GLP-1 R agonist to improve glycemic control and reduce CVD risk (Class III).

- **NO**
  - Does the patient have other CVD risk factors?

- **YES**
  - Further management of diabetes per primary care provider or endocrinology.

- **NO**
  - Reinforce the importance of diet and physical activity and continue current management.

Figure 2. ACC/AHA guidance on the treatment of type 2 diabetes for primary prevention of cardiovascular disease

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Advocating a patient-centred approach

In the ACC guidance, a patient-centred approach is recommended with shared decision-making guiding discussions about the best strategies to reduce atherosclerotic cardiovascular disease for that individual. “It is important that there is an ongoing conversation about the introduction of ‘protective classes of drugs’, such as an SGLT-2 inhibitor or a GLP-1 RA, early on in the therapy of at-risk diabetic patients.”

Evidence-based medicine (EBM) is defined as the ‘conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients’. However, EBM does not mean ‘cookbook medicine’. “Science can be used to inform clinical decisions, but cannot definitively inform value judgements, because the significance of potential benefits and harms of a therapy are in the eye of the beholder and will differ across individuals.” In the face of evolving knowledge and new evidence that benefits patients, newer therapies (SGLT-2 inhibitors and GLP-1 RAs) may benefit specific groups of patients. It is incumbent on physicians to share this knowledge with patients. New evidence often requires a change in the culture of a past way of doing things, and a ‘new culture’ can only prevail if there is repeated ongoing education, discussion and reflection on the change. Reflection and ongoing conversation will alleviate fear of new therapies and help in identifying those patients who would benefit most. Thus, objective assessment of individualised need is enhanced, improving benefit (beneficence) and reducing harm (non-maleficence). Education through communication remains the cornerstone of effective management of patients.

Goals of care

- Prevent complications
- Optimise quality of life

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

DSMES - Diabetes self-management education and support

Figure 3. ADA/EASD decision cycle for patient-centred management in type 2 diabetes

Patient autonomy in decision-making is dependent on correct understanding of the new evidence and the doctor needs to relate (communicate) this in a simple manner. The word ‘doctor’ derives from the Latin ‘docere’ which means ‘to teach’ or ‘to guide’.

Importantly, environmental and psychosocial factors including depression, stress, self-efficacy and social support should be evaluated for each patient so that suitable, allied healthcare professionals can be included in the team-based support of an individual patient. Interestingly, the latest clinical guidance from ADA/EASD shares this patient-centred approach.

This expert guidance is summarised in Figure 3 (adapted from ADA/EASD guideline).
The ADA/EASD guidance points to the pivotal role of recent data from cardiovascular outcome trials in the expanded use of GLP-1 RAs (Figure 4). In particular, a recent meta-analysis and the results from the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcomes Results (LEADER) trial, which showed a significant 13% relative risk reduction (RRR) in the three-point major adverse cardiac events (MACE) of cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke, have led to an emphasis on using these new agents. The LEADER trial (n=9340) demonstrated an absolute risk reduction of 1.9%, with a hazard ratio (HR) of 0.87 (95% CI 0.78, 0.97; P=0.01 for superiority) for MACE compared with placebo over 3.8 years. Each component of the composite contributed to benefit and the HR for cardiovascular death was 0.78 (95% CI 0.66, 0.93; P=0.007; ARR 1.7%). The LEADER trial also showed a HR of 0.85 (95% CI 0.74, 0.97; P=0.02; ARR 1.4%) for all-cause mortality.

Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RAs strongest evidence for liraglutide > semaglutide > exenatide extended release

For SGLT-2i evidence modestly stronger for empagliflozin > canagliflozin

Be aware that SGLT-2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use. Both empagliflozin and canagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs

CV, cardiovascular; DPP-4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide 1 receptor agonist; SGLT-2i, SGLT-2 inhibitor; SU; sulphonylurea; CVOTs; cardiovascular outcomes trials

Figure 4. ADA/EASD guidance stresses the selection of these glucose-lowering medications for those diabetics with established atherosclerotic cardiovascular disease
2018 ESC/ESH guidelines for hypertension in presence of diabetes

Interestingly the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) have also recognised the value of newer anti-diabetes agents, such as SGLT-2 inhibitors and GLP-1 RAs in their latest guidance. These guidelines note: “Two GLP-1 RAs (liraglutide and semaglutide) reduce cardiovascular risk and total mortality, but not heart failure in patients with type 2 diabetes.”

This hypertension-focused guidance advises the use of these agents as they reduce cardiovascular risk and lower blood pressure slightly; liraglutide also lowers body weight.

Commonality of these European/American guidelines

All three of these emphasise the cardiovascular benefits of GLP-1 RAs and SGLT-2 inhibitors. In addition, the ADA/EASD consensus document recommends that in patients who need the greater glucose-lowering effect of an injectable medication, GLP-1 RAs are preferred over insulin.

What do the SEMDSA diabetes management guidelines propose?

The 2017 Society of Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) guideline authors were anticipatory and expectant of the possibilities of these newer agents, despite all the recent cardiovascular outcome trial data not being available to them at the time of guideline compilation (Figure 5). As evidence was not yet published, SEMDSA recommendations are ‘indicative’ relative to the firmer, later guidance of international specialist organisations. The SEMDSA guidance on GLP-1 RAs notes the circumstances where a GLP-1 RA may be preferred over other treatment options; in patients with established cardiovascular disease (liraglutide benefit).

Figure 5. Initiating and titrating basal insulin therapy

*Adapted from SEMDSA 2017 Guidelines
The 2017 SEMDSA guidelines are for non-high-risk patients to be treated at primary healthcare level. It is correct that complicated patients and those on multiple therapies should ideally be managed at specialist care level. This is not to say that a primary care physician with adequate experience and knowledge of diabetes cannot prescribe the newer cardioprotective agents. One concern is misidentifying patients, i.e. prescribing newer cardioprotective agents to patients who do not fit the trial criteria in which said agent showed benefit. It is not uncommon for doctors to generalise on a benefit found in specific trial circumstances. Further, diabetic patients may present with many complexities. Identifying high-risk patients is the first step.

Various other factors need to be considered, however:

- Age
- Comorbidities, e.g. renal failure, cholestatic disease, UTI history, history of urological interventions
- Other medications
- Microvascular complications with autonomic dysregulation.

These and other complexities require astute clinical judgement to help tailor a diabetes treatment regimen beyond just the addition of a cardioprotective agent. Number needed to treat (NNT) and number needed to harm (NNH) should be considered along with cost and patient values. The time horizon to benefit also needs to be considered when considering prescriptions.

Avoiding overtreatment, drug interactions, side effects, hypoglycaemia and worsening of existing conditions requires careful analysis and consideration, probably best done under specialist care.

The approach should focus on how to get a high-risk patient onto the appropriate newer cardioprotective drug and at the same time address the above issues. The 2017 guidelines could, however, be updated to be more specific about current preferences in respect of cardioprotective agents and the circumstances under which they should be considered. A new table or diagrammatic representation that is easy to follow would be useful.

Further, it may be updated to provide clarity (in a simple tabulated form) to primary healthcare practitioners on identifying high-risk patients and how to refer them easily. Another suggested chapter in the guideline could address pitfalls in the management of diabetes such as adherence, physician inertia and the role of patient education that is less prescriptive and invites more critical thinking.
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References


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### 1. From the 2019 ESC Guidelines, patients at high risk for CVD are defined as:
- A DM duration >10 years without target organ damage but with any other additional risk factor
- B DM duration >10 years

### 2. 2019 ESC Guidelines recommend:
- A That GLP-1 RAs should be used first-line in T2DM with established or high risk of CVD
- B That the gliflozins should be used first-line in T2DM with established or high risk of CVD
- C Liraglutide is specifically recommended in patients with T2DM and established CVD or at very high risk
- D All the above
- E A and C

### 3. The ACC/AHA recommend that in the patient with T2DM and established atherosclerotic CVD, the clinician should prioritise:
- A Guideline-directed medical therapy including metformin, lifestyle, antiplatelet, blood pressure and lipids
- B Use of SGLT-2 inhibitor or GLP-1 RA with demonstrated CV outcomes benefit
- C A and B concurrently

### 4. Which of the following is false? In the patient with T2DM, measures for primary prevention of CVD includes:
- A BP <140/80mmHg
- B Low-dose aspirin for all T2DM patients
- C Moderate (≥150mins/week) or vigorous (≥75mins/week) physical activity
- D A and B
- E B and C

### 5. Patient education about the best strategies to reduce risk for atherothrombotic CVD should include:
- A Dietary counselling on a heart-healthy diet
- B Conversations about the introduction of cardioprotective drugs (SGLT-2 inhibitors, GLP-1 RAs)
- C A and B

### 6. Suitable team-based patient-centred care requires assessment of which environmental and psychosocial support factors?
- A Depression
- B Stress
- C Social support
- D Self-efficacy
- E All the above
- F A and C only

### 7. From meta-analysis of the LEADER trial, liraglutide demonstrated a significant RRR in three-point MACE of:
- A 13%
- B 1.9%

### 8. From meta-analysis of the LEADER trial, liraglutide demonstrated an absolute RR in three-point MACE of:
- A 10%
- B 1.9%

### 9. The Leader trial showed a HR of 0.78 (22% reduction) for cardiovascular death.
- A True
- B False

### 10. In T2DM patients at CVD risk, SGLT-2 inhibitors with proven CVD benefit can be used regardless of renal function.
- A True
- B False

### 11. Which of the following GLP-1 RAs reduces CV risk, slightly lowers blood pressure and lowers body weight?
- A Liraglutide
- B Semaglutide
- C Exenatide

### 12. Which SGLT-2 inhibitor has shown reduction in HF and reduction in CKD progression?
- A Empagliflozin
- B Canagliflozin
- C A and B

### 13. In patients at CVD risk not attaining HbA1c target on treatment with a GLP-1 RA, consider:
- A Adding a SGLT-2 inhibitor with proven CVD benefit
- B Adding a DPP-4 inhibitor
- C A and B

### 14. In patients at CVD risk not attaining HbA1c target on treatment with a GLP-1 RA or SGLT-2 inhibitor, which agents with demonstrated CV safety can be used for treatment intensification?
- A Basal insulin
- B TZD
- C Basal insulin
- D A and C

### 15. Factors for consideration in identifying high CV risk T2DM patients include:
- A Age
- B Comorbidities
- C Polypharmacy
- D Microvascular complication with autonomic dysregulation
- E All the above
- F B, C and D