ESC/EASD guideline sheds light on diabetes and cardiovascular disease management

In their latest guideline on managing cardiovascular disease in people with diabetes and prediabetes, the ESC and EASD have summarised and interpreted key evidence relevant to clinical practice. Steve Chaplin reports.

Just as the number of people with, or at risk of developing, diabetes grows inexorably, so it seems does the volume of clinical research on diabetes management. Clinicians who wonder how they will get to grips with all this information will welcome the third guideline on managing cardiovascular disease (CVD) in people with diabetes and prediabetes from the European Society of Cardiology (ESC), which it developed in collaboration with the European Association for the Study of Diabetes (EASD).¹ The 58-page document summarises and interprets key evidence published since the 2013 version, presenting its recommendations in clear, colour-coded tables. This is supported by no fewer than 579 references, and online resources will ultimately include a slide set, a pocket version, an app and questions for continuing medical education.

Overview
This ‘shorter, concise document’ aims ‘to provide information on the current state of the art in how to prevent and manage the effects of [diabetes] on the heart and vasculature’. Detailed guidance, if needed, should be sought in more specialised publications from the ESC (www.escardio.org) and the ADA (www.diabetes.org). It’s striking that the ESC/EASD guideline approaches the topic without strongly distinguishing between type 1 and type 2 diabetes (T1DM and T2DM), unlike the 2013 version. Like its predecessors, the guideline covers prediabetes and diagnosed diabetes. With obvious exceptions for measures to tackle lifestyle change and drug treatment, the recommendations focus on cardiovascular (CV) risk, not the underlying cause of dysglycaemia.

The document includes two features that should be compulsory for all guidelines. First is a table listing the changes since the 2013 guideline, with the old and new recommendations side by side. This immediately provides the reader with points of reference for deciding where change is needed to accommodate the new information – something that is often overlooked in the enthusiasm for presenting an intimidating bulk of data. Second is a full set of the recommendations in a ‘What to do’ ('Is recommended or indicated') and ‘What not to do’ ('Is not recommended') list. For the academically inclined, there is also the usual indication of strength of supporting evidence of ‘A’ (data from multiple randomised clinical trials or meta-analyses), ‘B’ (data from a single randomised clinical trial or large non-randomised studies) and ‘C’ (consensus opinion and/or small studies, retrospective studies, registries). Forty-one of the 77 recommendations are rated ‘A’ for strength of evidence; conversely, all the seven recommendations on the diagnosis and management of peripheral arterial disease are rated ‘C’.

Less impressive is the relegation of patient-centred care to the back of the document. Translational aspects of clinical practice have always lacked the glamour of clinical science but it’s a truism that if patients can’t be persuaded of the merits of treatment then all the expensive research goes to waste. This relatively brief section includes the important but easily overlooked statement that: ‘Patient-centred care is an approach that facilitates shared control and decision-making between patient and provider. It emphasizes a focus on the whole person and their experiences of illness within social contexts, rather than a single disease or organ system, and it develops a therapeutic alliance between patient and provider. It is also a care strategy that is respectful and responsive to individual patient preferences, needs, and values, and it places the patient as an “active drug” at the centre of care, working in collaboration with healthcare professionals.’ However, some of the language used in the guideline – for example, ‘young onset female individuals’ – suggests an unwelcome detachment from clinical realities. The evidence shows that group-based structured education, shared control and decision-making, and individual empowerment strategies are effective. It would be useful to have case studies on implementing the guideline recommendations using these strategies in the online resources.

Managing cardiovascular disease
The bulk of the guideline comprises seven sections on CVD: risk assessment; prevention; coronary artery disease; heart failure; arrhythmias; aortic and peripheral arterial diseases; and chronic kidney disease.

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk factors</th>
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<tbody>
<tr>
<td>Very high risk</td>
<td>Patients with DM and established cardiovascular disease or other target organ damage* or three or more major risk factors** or early onset T1DM of long duration (&gt;20 years)</td>
</tr>
<tr>
<td>High risk</td>
<td>Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>Young patients (T1DM aged &lt;35 years or T2DM aged &lt;50 years) with DM duration &lt;10 years, without other risk factors</td>
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DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus. *Proteinuria, renal impairment defined as eGFR <30ml/min/1.73m², left ventricular hypertrophy, or retinopathy. **Age, hypertension, dyslipidaemia, smoking, obesity.

Table 1. Cardiovascular risk categories in people with diabetes. (Reproduced from: © The European Society of Cardiology 2019)
Risk assessment
Cardiovascular risk is raised in everyone with diabetes (Table 1). The strongest recommendations are for routine assessment of microalbuminuria to identify patients at risk of developing renal dysfunction or at high risk of future CVD, and for a resting ECG in patients diagnosed with hypertension or with suspected CVD. Other tests (echocardiography, coronary artery calcium score, ankle-brachial index) fall under the ‘may be considered’ banner. Routine assessment of novel biomarkers to assess CV damage is not recommended for CV risk stratification, nor are risk scores developed for the general population.

Gaps in knowledge include the prognostic value of advanced imaging techniques and whether it’s worthwhile imaging coronary artery stenoses or to treat them aggressively. Too little is known about sex-specific differences in coronary artery disease (CAD) diagnosis and the uptake of risk assessment in different ethnic groups.

Prevention of cardiovascular disease
This large section of the guideline (second only to CAD) covers lifestyle change, glucose control, blood pressure, lipid-lowering therapy and antiplatelet therapy, which should be combined in a multifactorial approach. Treatment targets are specified for at least some people with diabetes for control of glucose, blood pressure and lipids (Table 2).

Lifestyle change is, as all similar guidelines state and people with diabetes appear to find most challenging, the key to preventing diabetes and its CV complications. The DiRECT trial, which showed that severe calorie restriction and weight loss can achieve remission or avoid drug treatment in people with T2DM, reinforces both points. The recommendations on diet, physical activity and smoking cessation are familiar but it’s useful to be reminded that neither moderate alcohol consumption nor nutritional supplements are the path to CV risk reduction. The scientific jury is still out on the merits of e-cigarettes (though the evidence is rapidly evolving and public health officials are concerned). More work is needed to determine how to increase adherence to lifestyle change, how to address cultural determinants of diet and what lifestyle changes are appropriate for different age groups.

The target for glycaemic control – HbA1c <55mmol/mol, with younger people benefiting from a lower target – is more relaxed than NICE’s current position (encourage a target of <48mmol/mol, or <53mmol/mol if taking glucose-lowering therapy). The purpose of this target, which should be individualised according to duration of diabetes, age and comorbidity, is to minimise the risk of microvascular and possibly macrovascular complications. This must be balanced against the risk of hypoglycaemia, which most studies show is associated with adverse CV events. Self-monitoring of blood glucose and/or continuous glucose monitoring should be ‘considered’ though in the UK it is recommended for everyone with T1DM and some people with T2DM.

Raising systolic pressure should be lowered to <130mmHg if tolerated (but not <120mmHg), or 130–139mmHg in people aged >65, with diastolic pressure lowered to <80mmHg (not <70mmHg). This differs from NICE guidance which is the same as for the general population for T2DM – i.e. 140/90mmHg – and 135/85mmHg or 130/80mmHg for T1DM, depending on comorbidity. This should be achieved by lifestyle change and treatment initially using dual therapy with an ACE inhibitor or angiotensin receptor blocker plus an aldosterone system blocker, calcium channel blocker or a diuretic. Self-monitoring of blood pressure should be encouraged (NICE’s stance is neutral). Current known unknowns include the impact of SGLT2 inhibitors and...
GLP-1 analogues on blood pressure management and optimal targets for some people with diabetes.

ESC/EASD specifies several targets for LDL-C level for people with T2DM depending on their CV risk, and a reduction of 50% from baseline (NICE advises a risk-based approach and a reduction of 40%). There are no targets for people with T1DM but treatment should be considered in those at high risk. A statin is the treatment of choice, individualised with an intensive dose if necessary. If this is ineffective, ezetimibe should be added with the monoclonal alirocumab another option, though experience is limited.

Antiplalet therapy should be the same for people with diabetes as for anyone else, meaning a cautious approach with aspirin as primary prevention: it ‘may’ be considered for people with high/very high risk but it is not recommended for people at moderate risk. As for secondary prevention, the drug of choice is aspirin 75–100mg/day plus a proton pump inhibitor, with a second antiplatelet agent if needed.

Coronary artery disease management
Reflecting the CV perspective of the guideline, this section provides an in-depth review of recent evidence of the benefits of early intensive glycaemic control and the impact of glucose-lowering therapies. The importance of this approach is supported by evidence that blood glucose abnormalities are common in patients with acute and stable CAD and linked with a poor prognosis. Further, 20–30% of people with CAD have a diagnosis of diabetes and up to 70% of the remainder are found to have prediabetes or diabetes when tested.

There is now strong evidence that the SGLT2 inhibitors (empagliflozin, canagliflozin, dapagliflozin) and GLP-1 analogues (lixisenatide, semaglutide, dulaglutide) reduce CV events in people with diabetes who have or are at high/very high risk of CVD, for whom these agents are recommended to reduce the risk of CV events or death (depending on what the trials show for different drugs). Metformin now ‘should be considered’ for overweight patients with T2DM who have a moderate risk of CVD or no CVD. Insulin is an option for people with acute coronary syndrome and significant hyperglycaemia. Saxagliptin is not recommended in patients with T2DM and heart failure, and heart failure is a contraindication to pioglitazone. The guideline includes a complex algorithm to guide the choice of glucose-lowering drugs for people with T2DM according to the current treatment with metformin, presence of atherosclerotic disease and risk factors.

Recommendations on specific CV therapies will prompt the average general clinician to seek specialist advice. For example, beta blockers have an established role after myocardial infarction but they may increase all-cause deaths in people with diabetes; and ranolazine and ivabradine, proposed second-line agents for angina, are considered third-line in the UK.

Heart failure
Heart failure increases the risk of diabetes, and vice versa. Together they increase the risk of hospitalisation and all-cause and CV death but treatment for heart failure is not altered by the presence of diabetes. Of the glucose-lowering drugs, SGLT2 inhibitors are recommended to reduce the risk of hospitalisation (though quite how they improve outcomes awaits clarification). Metformin and the GLP-1 analogues have a neutral effect. There is uncertainty about the safety of DPP-4 inhibitors in people with heart failure: saxagliptin is associated with adverse outcomes whereas sitagliptin and linagliptin are not and the evidence is not definitive for alogliptin and vildagliptin. The evidence for sulphonylureas is conflicting, and pioglitazone is not recommended in symptomatic patients.

Arrhythmias, aortic and peripheral arterial disease
Atrial fibrillation is common in people with diabetes and is associated with increased mortality, including sudden cardiac death, stroke and heart failure; hypo-glycaemia can trigger arrhythmias. Although recent evidence suggests young people are at risk, the guideline recommends screening only for the over-65s. Treatment options include antiocoagulation with a novel oral anticoagulant in the presence of atrial fibrillation, and a beta blocker for patients with heart failure or after myocardial infarction with reduced left ventricular fraction.

The coexistence of diabetes worsens the prognosis for someone with peripheral arterial disease. Management is the same as in the absence of diabetes, though outcomes after revascularisation are poorer. Carotid artery disease, which underlies 10–15% of strokes, is usually managed conservatively if the patient is asymptomatic but revascularisation is an option in the presence of risk factors or advanced stenosis. People with diabetes have an increased risk of restenosis, perioperative stroke and death.

Chronic kidney disease
People with CKD and diabetes should be considered in the highest risk category for CVD. Blood pressure control (to <130mmHg systolic but not <120mmHg) and intensive glycaemic control (<53mmol/mol) may slow progression and the choice of treatment is limited to drugs without significant renal excretion such as insulin and the GLP-1 analogues. Patients with early CKD and diabetes may benefit from treatment with an SGLT2 inhibitor – for example, canagliflozin has been shown to reduce the combined risk of end-stage renal disease, doubling of serum creatinine levels, or renal or CV death by 30% in patients with eGFR 30 to <90ml/min/1.73m².

Summary
The 2019 ESC/EASD guideline is a comprehensive and detailed update on the management of CVD in people with diabetes or prediabetes. It offers an exhaustive analysis of current evidence and, at a time when guidelines abound, it sets the benchmark for authoritative scientific advice. Its recommendations do not always coincide with NICE guidance and clinicians will need to decide which are preferable and achievable.

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References