Diabetes and cardiac health

Challenges to risk assessment and prevention strategies

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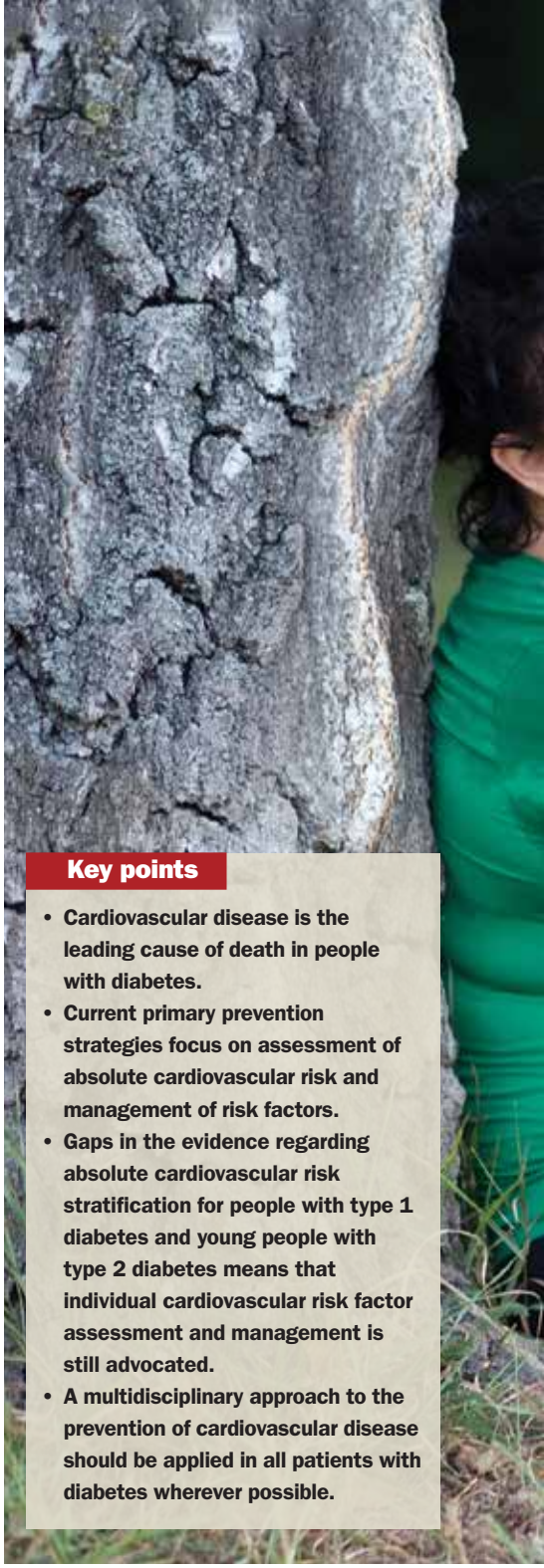
Current recommendations for primary prevention of cardiovascular disease promote risk stratification and management based on estimation of absolute cardiovascular risk. However, this approach has not been adequately tested in people with type 1 diabetes or young people with type 2 diabetes, who may have a longer lifetime exposure to suboptimal cardiovascular risk factors and will therefore require an individualised management approach.



Key points

- **Cardiovascular disease is the leading cause of death in people with diabetes.**
- **Current primary prevention strategies focus on assessment of absolute cardiovascular risk and management of risk factors.**
- **Gaps in the evidence regarding absolute cardiovascular risk stratification for people with type 1 diabetes and young people with type 2 diabetes means that individual cardiovascular risk factor assessment and management is still advocated.**
- **A multidisciplinary approach to the prevention of cardiovascular disease should be applied in all patients with diabetes wherever possible.**

Cardiovascular disease (CVD) is the leading cause of death in Australia among patients with diabetes.[1,2] In response to the pervasive nature of CVD, particularly in high-risk groups such as people with diabetes, the National Vascular Disease Prevention Alliance (NVDPA) comprised of Diabetes Australia, the National Heart Foundation of Australia, Kidney Health Australia and the National Stroke Foundation was formed with a shared vision to reduce the burden of CVD.[1] This alliance has been instrumental in drawing focus to the absolute risk stratification paradigm for CVD management in Australia. This move is echoed internationally with the acknowledgement that multiple risk factors contribute to an individual's overall absolute CVD risk synergistically rather than in an additive fashion.[3,4]

This article discusses primary prevention of CVD using absolute risk stratification, as well as addressing gaps in the evidence relating to people with type 1 diabetes and young people with type 2 diabetes. Individualisation of management targets and the role of new glucose-lowering therapies are also addressed.

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Calculating CVD risk in diabetes

An Australian risk calculator (available online at www.cvdcheck.org.au) was developed by the NVDPA in 2012 using the Framingham Risk Equation.[1] In adults 45 years of age and older (or ≥35 years for Aboriginal and Torres Strait Islander people), this calculator estimates the absolute risk of a first cardiovascular event over the next five years.[1] The estimated absolute risk is then

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stratified as high (>15% risk), moderate (10 to 15% risk) or low (<10% risk) to guide risk-factor management.[1]

As part of a comprehensive risk assessment (Box 1), the Australian risk calculator helps to develop tailored approaches to subsequent management.[1] However, some patients are already known to be at high absolute risk of CVD and can be managed accordingly without a numerical estimation of absolute risk (see Box 2).[1,5,6] The key components of CVD management are lifestyle changes, pharmacotherapy, treatment targets, monitoring clinical parameters and calculating absolute risk.[1] Optimal lifestyle behaviours, including smoking cessation, adherence to dietary and physical activity recommendations and avoiding excessive alcohol intake, are recommended for all patients regardless of the level of absolute risk.[1] In contrast, use of pharmacotherapy is introduced depending on the level of risk, with emphasis on the central role of lipid lowering with statin therapy (Box 3) and blood pressure lowering with blockade of the renin–angiotensin–aldosterone system particularly for patients with diabetes (Box 4).[1] A detailed discussion of management strategies can be found in the NVDPA's guidelines on the management of absolute cardiovascular risk.[1]

1. Comprehensive risk assessment in adults without known CVD[1]

During a comprehensive risk assessment, the following risk factors and related conditions should be considered

Modifiable risk factors

- Smoking status
- Blood pressure
- Serum lipid levels
- Waist circumference and body mass index
- Nutrition
- Physical activity level
- Alcohol intake

Nonmodifiable risk factors

- Age
- Sex
- Family history of premature CVD
- Social history (e.g. cultural identity, ethnicity and socioeconomic status)

Related conditions

- Diabetes
- Chronic kidney disease (albuminuria with or without urine protein, estimated glomerular filtration rate)
- Familial hypercholesterolaemia
- Evidence of atrial fibrillation (history, examination, electrocardiogram)

Abbreviation: CVD = cardiovascular disease.

Adapted from National Vascular Disease Prevention Alliance. Guidelines for the management of absolute cardiovascular disease risk; 2012.[1]

Challenges to CVD risk assessment and prevention strategies in diabetes

Diabetes approximately doubles the risk of developing CVD.[1] However, although the contribution of diabetes per se to increased

2. Adults known to be at high absolute risk of CVD[1]

- Diabetes and age >60 years
- Diabetes with microalbuminuria (>20 mcg/min or urinary albumin: creatinine ratio >2.5 mg/mmol for men, >3.5 mg/mmol for women)
- Moderate or severe chronic kidney disease (persistent proteinuria or estimated glomerular filtration rate <45 mL/min/1.73 m^2)
- A previous diagnosis of familial hypercholesterolaemia
- Systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg
- Serum total cholesterol level >7.5 mmol/L

Abbreviation: CVD = cardiovascular disease.

Adapted from National Vascular Disease Prevention Alliance. Guidelines for the management of absolute cardiovascular disease risk; 2012.[1]

3. Management of dyslipidaemia[1]

- Statins should be used as first-line therapy
- If low-density lipoprotein cholesterol levels are not sufficiently reduced while taking maximally tolerated dose of a statin, one or more of the following may be added:
  - ezetimibe
  - bile acid binding resin
  - nicotinic acid
- If statins cannot be tolerated, one or more of the following may be used:
  - ezetimibe
  - bile acid-binding resin
  - nicotinic acid
- If triglyceride levels remain elevated, treatment with one of the following may be considered:
  - fenofibrate (especially if high-density lipoprotein level is below target)
  - nicotinic acid
  - fish oil

Adapted from National Vascular Disease Prevention Alliance. Guidelines for the management of absolute cardiovascular disease risk; 2012.[1]

4. Management of hypertension in people with diabetes[1]

- Blood pressure-lowering therapy should preferentially include an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker
- If monotherapy does not sufficiently reduced blood pressure, one of the following should be added:
  - calcium channel blocker
  - low-dose thiazide or thiazide-like diuretic

Adapted from National Vascular Disease Prevention Alliance. Guidelines for the management of absolute cardiovascular disease risk; 2012.[1]

cardiovascular risk is well established, the intensity and method by which to manage glycaemic control and its impact on absolute risk continues to be debated.

Use of CVD risk calculators

Much of the existing guidance on CVD risk stratification and management of people with type 1 diabetes or those with type 2 diabetes aged under 45 years is based on evidence from mid-to-older aged populations with type 2 diabetes.[7-11] The risk calculator developed by the NVDPA uses the Framingham Risk Equation which has been reported to be a poor predictor of events in patients with type 1 diabetes, and to generally underestimate CVD risk in populations with diabetes.[1,5,6] It also lacks consideration of the duration of exposure to various risk factors which may be of particular relevance to younger patients.[9] Furthermore, the calculator is not applicable to people under 45 years of age (or <35 years for Aboriginal or Torres Strait Islander people).[1] This is an issue as people with type 1 diabetes experience cardiovascular events about 10 years earlier than a matched population without diabetes, and have an age-adjusted relative risk of CVD of up to 10 times that of the general population.[9]

Current guidelines are therefore unable to provide an adequate approach to risk stratification and management for people with type 1 diabetes or those with type 2 diabetes younger than 45 years of age. A practical approach may be to acknowledge gaps in the evidence and recognise that applying the risk calculator to these groups will provide at most a conservative estimate of absolute CVD risk. In combination with clinical judgment, specialist referral and individual patient preferences, CVD risk factors may then be addressed using a tailored approach.

Effects of intensity of glycaemic control

The role of intensive therapy to lower blood glucose levels in patients with type 2 diabetes has yielded moderate benefits with regards to CVD. This is notable by comparison to patients with type 1 diabetes in whom there is strong evidence of substantial benefits.

The landmark Diabetes Control and Complications Trial (DCCT) and follow up Epidemiology of Diabetes Interventions and Complications (EDIC) study have led the call for intensive management of glycaemia for all patients with type 1 diabetes after reporting clear reductions in microvascular complications and cardiovascular events persisting after 30 years of follow up.[12,13]

In contrast, the United Kingdom Prospective Diabetes Study (UKPDS) investigating the effects of more versus less intensive glycaemic control (achieving an HbA_{1c} of 7.0% *vs* 7.9% [53 *vs* 63 mmol/mol] at the end of follow up) in patients with newly diagnosed type 2 diabetes did not demonstrate a significant reduction in CVD events at the completion of the trial.[14,15] However, after an additional observational follow up of 10 years, a significantly decreased risk of myocardial infarctions and death from any cause were observed.[14]

Further trials of patients with type 2 diabetes, including the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial and the Veterans Affairs Diabetes Trial (VADT), have failed to separately demonstrate clear benefit of more (targeting HbA_{1c} levels <6.5% [<48 mmol/mol]) versus less intensive glycaemic control on cardiovascular outcomes.[16-19] Quite unexpectedly,

the ACCORD trial also reported increased mortality risk with more intensive therapy.[17] Results combined in subsequent meta-analyses demonstrated a modest reduction in risk of major CVD events and microvascular complications without significant impact on all-cause mortality.[19,20]

Taken together the findings of these randomised trials as well as the management strategies used may be important for individualisation of glucose management. For example, intensive therapy after diagnosis may be safer than later on, caution may need to be applied to the speed of glycaemic improvement in older patients, hypoglycaemia may limit titration of therapy, and weight gain with therapy intensification may be counterproductive when managing cardiovascular risk.[16-19] Overall, an intensive approach to glycaemic control reduces risk of CVD regardless of diabetes type, and should be offered to most patients with type 1 and many patients with type 2 diabetes.

Table 1. Individualising HbA_{1c} targets in adults with type 2 diabetes*[32]

Specific clinical situations	Therapy	HbA_{1c} targets
Diabetes of short duration and no clinical cardiovascular disease	Requiring lifestyle modification plus metformin	≤6.0% (≤42 mmol/mol)†
	Requiring any antidiabetic agents other than metformin or insulin	≤6.5% (≤48 mmol/mol)†
	Requiring insulin	≤7.0% (≤53 mmol/mol)†
Pregnancy or planning pregnancy	–	≤6.0% (≤42 mmol/mol)†
Diabetes of longer duration‡ or clinical cardiovascular disease	Any	≤7.0% (≤53 mmol/mol)†
Recurrent severe hypoglycaemia or hypoglycaemia unawareness	Any	≤8.0% (≤64 mmol/mol)†
Patients with major comorbidities likely to limit life expectancy§	Any	Symptomatic therapy of hyperglycaemia‖

* General target HbA_{1c} level for all patients with type 2 diabetes is ≤7.0% (≤53 mmol/mol).
† Achievement of HbA_{1c} targets must be balanced against risk of severe hypoglycaemia, especially in the elderly.
‡ In an older adult, long duration might be considered to be more than 10 to 20 years, but for a person who develops type 2 diabetes at a young age, it may be considerably longer.
§ Examples of major comorbidities include chronic medical conditions such as chronic kidney disease stages 4 or 5; New York Heart Association heart failure stages III or IV; incurable malignancy; and moderate-to-severe dementia.
‖ If practical, suggest blood glucose target of <15.0 mmol/L to help minimise risk of infection.
Adapted from Cheung NW, et al. Position statement of the Australian Diabetes Society: individualisation of glycated haemoglobin targets for adults with diabetes mellitus. Med J Aust 2009; 191: 339-344.[32]

The role of new glucose-lowering therapies in type 2 diabetes

More recent trials are reporting cardiovascular benefit of some glucose-lowering therapies, independent of glycaemic impact.[21] Rather than considering primary prevention of CVD most of these studies have been designed as noninferiority trials to determine cardiovascular safety in patients with pre-existing CVD and type 2 diabetes. Perhaps the strongest evidence for cardiovascular benefit comes from the Empagliflozin, Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial.[22] Not only did empagliflozin meet the prespecified noninferiority margin for cardiovascular safety, but it also demonstrated reduced cardiovascular and all-cause mortality.[22] Empagliflozin has subsequently become the first oral antihyperglycaemic agent to receive Therapeutic Goods Administration approval for the prevention of cardiovascular death.[23]

Promising results also come from the Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes (CANVAS) Program.[24] In patients with pre-existing CVD or in those at high cardiovascular risk (≥50 years of age with two or more trial-defined risk factors), canagliflozin met both noninferiority and superiority margins for the primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke.[24] However, concerns regarding increased rates of foot amputation and fracture are being further examined as well as differences among the agents within the class of sodium glucose cotransporter-2 inhibitors.[24]

Glucagon-like peptide-1 (GLP-1) receptor agonists have also demonstrated cardiovascular safety, and perhaps a role in CVD secondary prevention.[21] The Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes (LEADER), Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6), and Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome (ELIXA) trials met their respective noninferiority margins, with the former two trials reporting reduced cardiovascular morbidity in people with pre-existing CVD (semaglutide is currently not available in Australia).[25-27] However, only the LEADER study was powered to demonstrate superiority.[25] A recent meta-analysis of 189 trials of incretin-based therapies has reported the possibility of a mortality benefit with use of GLP-1 agonists.[28] Tempered by a potential negative impact on microvascular complications and inconsistent CVD findings, further studies aim to clarify the role of GLP-1 agonists beyond improvements in glycaemia and weight reduction.[21]

Table 2. Individualising HbA_{1c} targets in adults with type 1 diabetes*[32]

Specific clinical situations	HbA_{1c} target
Pregnancy or planning pregnancy	≤7.0% (≤53 mmol/mol)††
Recurrent severe hypoglycaemia or hypoglycaemia unawareness	≤8.0% (≤64 mmol/mol)
Patients with major comorbidities likely to limit life expectancy	Symptomatic therapy of hyperglycaemia§ and avoidance of ketosis

* General target HbA_{1c} level for all patients with type 1 diabetes is ≤7.0% (≤53 mmol/mol).
† Achievement of HbA_{1c} targets must be balanced against risk of severe hypoglycaemia.
† An HbA_{1c} ≤6.0% (≤42 mmol/mol) is desirable if it can be achieved safely.
§ If practical, suggest blood glucose target of <15.0 mmol/L to help minimise risk of infection.

Adapted from Cheung NW, et al. Position statement of the Australian Diabetes Society: individualisation of glycated haemoglobin targets for adults with diabetes mellitus. Med J Aust 2009; 191: 339-344.[32]

5. Useful online resources on cardiovascular health and diabetes

- Royal Australian College of General Practitioners
  - Clinical guidelines for managing cardiovascular risk in diabetes (see: www.racgp.org.au/your-practice/guidelines/diabetes/9-managing-cardiovascular-risk/)
- Focus on Australian absolute risk stratification and risk factor management
  - The National Vascular Disease Prevention Alliance website, which includes CVD risk calculator and full management guidelines (see: www.cvdcheck.org.au/)
- Focus on diabetes
  - Position statements by the Australian Diabetes Society (see: http://diabetessociety.com.au/position-statements.asp)
  - A new blood glucose management algorithm for type 2 diabetes (see: http://t2d.diabetessociety.com.au)
- Focus on blood pressure and lipid profile
  - The Heart Foundation provides clinical information links for professionals to relevant guidelines (see: www.heartfoundation.org.au/for-professionals/clinical-information/)

Individual targets

Although an integrated approach to absolute CVD risk is advocated, it should not occur at the expense of management of individual risk factor levels.[1] Increasing blood pressure, high cholesterol levels and poor glycaemic control, for example, each have independently positive associations with cardiovascular risk.[1] Therefore, although management decisions should focus on the over-arching 'absolute risk' profile, monitoring should also focus on individual risk factor levels.[1] These need to be tailored to each patient considering the benefits and risks, as well as patient acceptability.

Important changes to recommendations on treatment include the more relaxed optimal blood pressure target (<140/90 mmHg) and the individualisation of HbA_{1c} targets.[29] However, consideration must be given to the need for lower blood pressure targets in younger patients with diabetes, patients with albuminuria and patients at high risk of stroke.[29,30] Similarly, consideration must be given to the need for lower HbA_{1c} targets for patients with type 1 diabetes, younger patients with type 2 diabetes and women with diabetes who are of reproductive age planning pregnancy,[31,32] as well as higher HbA_{1c} targets for patients with frequent or severe hypoglycaemia, those with comorbidities and those who are frail (Tables 1 and 2).[29,32]

A multidisciplinary care approach

The Royal Australian College of General Practitioners have published guidelines and a structured patient-centred care plan to facilitate an integrated approach to diabetes management as well as cardiovascular risk assessment.[29] Further discussion of management strategies can be found in the NVDPA guidelines for the management of absolute cardiovascular risk.[1] Referral of complex patients to relevant subspecialist physicians and allied healthcare professionals may also assist in addressing relevant CVD risk factors and aid risk stratification. This may be of particular relevance to patients whose care is not directly addressed by current guidelines and relies more on integration and communication of developing evidence as it pertains to the care of individual patients.

Conclusion

Prevention of CVD has moved to a paradigm of risk stratification and management based on estimation of absolute cardiovascular risk. Diabetes is a major driver of CVD and by virtue of its multisystem effects requires a broad and comprehensive management strategy (see Box 5 for some useful online resources). Available evidence has led to the development of absolute cardiovascular risk calculators that provide a good approach to stratifying risk. Patients with type 1 diabetes and young patients with type 2 diabetes may require particular consideration and a more individualised approach. Given the complex interplay between different risk factors and treatments in patients with diabetes, a multidisciplinary team approach is advocated. **ET**

References

A list of references is included in the online version of this article (www.endocrinologytoday.com.au).

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