

Type 2 diabetes and cardiovascular risk

Recommendations

Recommendation	Reference	Grade*
Assessing cardiovascular disease risk		
Calculate cardiovascular disease (CVD) risk level using an evidence-based tool, for example: <ul style="list-style-type: none"> • Australian absolute cardiovascular disease risk calculator • Australian cardiovascular risk charts 	RACGP Diabetes Handbook working groups, 2020	Consensus
Adults with any of the following conditions do not require absolute CVD risk assessment using the Framingham risk equation because they are already known to be at clinically determined high risk of CVD: <ul style="list-style-type: none"> • diabetes and aged >60 years • diabetes with microalbuminuria (>20 mcg/min or urine albumin-to-creatinine ratio [UACR] >2.5 mg/mmol for men and >3.5 mg/mmol for women) • moderate or severe chronic kidney disease (persistent proteinuria or estimated glomerular filtration rate [eGFR] <45 mL/min/1.73 m²) • a previous diagnosis of familial hypercholesterolaemia • systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg • serum total cholesterol >7.5 mmol/L 	1 NVDPA, 2012	D
Aboriginal and Torres Strait Islander peoples are generally assumed to be at higher risk	1 NVDPA, 2012	D
Patients with pre-existing CVD are at high risk	2 Baker IDI, 2015	None given
Managing CVD risk		
Adults at high absolute risk of CVD should be simultaneously treated with lipid and blood pressure-lowering pharmacotherapy in addition to lifestyle advice, unless contraindicated or clinically inappropriate	1 NVDPA, 2012	B
Sodium glucose co-transporter 2 (SGLT2) inhibitors are recommended in patients with type 2 diabetes in the setting of CVD and insufficient glycaemic control despite metformin, to decrease the risk of cardiovascular events and decrease the risk of hospitalisation for heart failure	3 Heart Foundation, 2018	Strong; high-quality evidence
Antihypertensive medication		
Antihypertensive therapy is strongly recommended in patients with diabetes and systolic blood pressure ≥140 mmHg	4 Heart Foundation, 2016	Strong; level I evidence
In patients with diabetes and hypertension, any of the first-line antihypertensive drugs that effectively lower blood pressure are recommended	4 Heart Foundation, 2016	Strong; level I evidence
In patients with diabetes and hypertension, a blood pressure target of <140/90 mmHg is recommended	4 Heart Foundation, 2016	Strong; level I evidence
A systolic blood pressure target of <120 mmHg may be considered for patients with diabetes in whom prevention of stroke is prioritised	4 Heart Foundation, 2016	Weak
In patients with diabetes where treatment is being targeted to <120 mmHg systolic, close follow-up is recommended to identify treatment-related adverse effects including hypotension, syncope, electrolyte abnormalities and acute kidney injury	4 Heart Foundation, 2016	Strong

Recommendation	Reference	Grade*
Lipid-lowering medications		
Use statins as first-line for lipid-lowering therapy	1 NVDPA, 2012	A
All adults with type 2 diabetes and known prior CVD (except haemorrhagic stroke) should receive the maximum tolerated dose of a statin, irrespective of their lipid levels Note: The maximum tolerated dose should not exceed the maximum available dose (eg 80 mg atorvastatin, 40 mg rosuvastatin)	2 Baker IDI, 2015	A
In people with type 2 diabetes and known prior CVD, fibrates should be commenced in addition to a statin or on their own (for those intolerant to statin) when fasting triglycerides are greater than or equal to 2.3 mmol/L, or high-density lipoprotein cholesterol (HDL-C) is low† Note: When used in combination with statins, fenofibrate presents a lower risk of adverse events than other fibrates combined with statins	2 Baker IDI, 2015	B
For adults with type 2 diabetes and known prior CVD already on maximally tolerated statin dose or intolerant of statin therapy, if fasting low-density lipoprotein cholesterol (LDL-C) levels remain ≥ 1.8 mmol/L, consider commencing one of: <ul style="list-style-type: none"> ezetimibe bile acid binding resins, or nicotinic acid 	2 Baker IDI, 2015	Consensus
Antithrombotic medication		
All adults with type 2 diabetes and known prior CVD should receive long-term antiplatelet therapy unless there is a clear contraindication	2 Baker IDI, 2015	A
All adults with type 2 diabetes and a history of ischaemic stroke or transient ischaemic attack should receive: <ul style="list-style-type: none"> low-dose aspirin, or clopidogrel, or combination low-dose aspirin and extended-release dipyridamole 	2 Baker IDI, 2015	A A B
Patients with a history of stroke and non-valvular atrial fibrillation who have adequate renal function should be initiated on direct oral anticoagulants (DOACs) in preference to warfarin	5 Stroke Foundation, 2019	Strong recommendation
All adults with type 2 diabetes and recent acute coronary syndrome and/or coronary stent should receive, for 12 months after the event or procedure: <ul style="list-style-type: none"> combination low-dose aspirin and clopidogrel, or combination low-dose aspirin and prasugrel, or combination low-dose aspirin and ticagrelor 	2 Baker IDI, 2015	B B C
All adults with type 2 diabetes and a history of coronary artery disease, but no acute event in the past 12 months, should receive <ul style="list-style-type: none"> long-term low-dose aspirin, or long-term clopidogrel if intolerant to aspirin 	2 Baker IDI, 2015	A B
In the presence of atrial fibrillation or other major risk factors for thromboembolism, there should be consideration of anticoagulant therapy according to other relevant guidelines	2 Baker IDI, 2015	Practice Point
*Refer to ' Explanation and source of recommendations ' for explanations of the levels and grades of evidence.		
†HDL < 1.0 mmol/L (based on the cut-offs reported in the ACCORD and FIELD studies)		

Clinical context

Cardiovascular disease (CVD) is the leading cause of death in people with diabetes, making assessment, prevention and management of CVD risk a vital part of diabetes care.

It is important to note that although myocardial infarction and stroke are commonly used as primary outcomes in type 2 diabetes trials, other common manifestations of CVD in people with type 2 diabetes are in fact peripheral arterial disease and heart failure.⁶ General practitioners (GPs) therefore need to consider these risks when addressing CVD risk in patients with type 2 diabetes.

Assessment of CVD risk

Assessment of combined multiple risk factors (absolute CVD risk) is more accurate than the use of individual risk factors.¹

All patients with type 2 diabetes should be assessed for absolute CVD risk, using a validated tool, at diagnosis. Note that all patients with type 2 diabetes and existing CVD are considered to be at high risk for another event.²

Depending on level of risk, patients should be reassessed at the following intervals:

- low absolute risk (<10%): every two years
- moderate risk (10–15%): every 6–12 months
- high risk (>15%): as clinically indicated.⁷

Absolute CVD risk assessment tools are available from:

- National Vascular Disease Prevention Alliance – [Australian absolute cardiovascular disease risk calculator](#)
- New Zealand Ministry of Health – [cardiovascular risk charts](#)
- [National Heart Foundation of New Zealand](#).

Coronary artery calcium (CAC) scoring: the clinical utility of CAC scoring in this situation is controversial and under current review.

People with type 2 diabetes and any of the following are already known to be at clinically determined high risk of CVD and **do not** require absolute CVD risk assessment:¹

- aged >60 years
- pre-existing CVD
- microalbuminuria (>20 mcg/min or urine albumin-to-creatinine ratio [UACR] >2.5 mg/mmol for men and >3.5 mg/mmol for women)
- moderate or severe chronic kidney disease (persistent proteinuria or estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m²)
- a previous diagnosis of familial hypercholesterolaemia
- systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg
- serum total cholesterol >7.5 mmol/L.

Aboriginal and Torres Strait Islander people aged >74 years are also generally assumed to be at high risk of CVD. Refer to The Royal Australian College of General Practitioners' (RACGP's) *National guide to a preventive health assessment for Aboriginal and Torres Strait Islander people*, [Chapter 11: Cardiovascular disease prevention](#).

Prevention and management of CVD

Interventions to manage CVD risk include:

- [lifestyle modification](#)
- [antihypertensive medication](#)
- [lipid-lowering medication](#)
- [antithrombotic therapy](#)
- [glucose-lowering medications that show novel non-glycaemic effects.](#)

In addition to lifestyle modification, **all people at high absolute CVD risk** should be treated with both antihypertensive medication and lipid-lowering medication (refer below), unless contraindicated or clinically inappropriate.¹

GPs should set individual treatment targets for patients, balancing the benefits and risks of interventions. For example, the CVD risk associated with lipid and blood pressure levels is continuous; hence, specific targets are somewhat arbitrary and should be used as a guide to treatment, not as mandatory goals. It's important to understand that there might be small absolute benefits required to reach suggested goals. However, any reduction in risk factor values will be associated with some benefit.¹

When developing a management plan for patients, refer to the National Vascular Disease Prevention Alliance's *Guidelines for the management of absolute cardiovascular disease risk*.¹

Lifestyle modification

Lifestyle changes in nutrition, physical activity and smoking status underpin a general practice approach to CVD risk minimisation. Lifestyle changes show excellent cost-effectiveness in lowering the burden of disease and remain the basis for the management of all CVD risk levels.^{8,9}

In people with type 2 diabetes and obesity (average BMI 36 kg/m²), the Look AHEAD study found that a lifestyle intervention that focused on weight loss improved glycated haemoglobin (HbA1c) and quality of life, but did not significantly reduce risk of cardiovascular morbidity or mortality.¹⁰

For further information, refer to the section '[Lifestyle interventions for management of type 2 diabetes](#)'.

Antihypertensive medication

Lowering blood pressure reduces cardiovascular events and all-cause mortality in people with type 2 diabetes. While no difference is noted between different classes of blood pressure-lowering therapy for CVD outcomes, there is clear evidence that in people with type 2 diabetes, antihypertensive therapy with an angiotensin receptor blocker (ARB) or angiotensin-converting enzyme inhibitor (ACEI) decreases the rate of progression of albuminuria, promotes regression to normoalbuminuria and may reduce the risk of decline in renal function. Combining an ARB and an ACEI is not recommended.^{1,11}

Blood pressure targets

The target level for optimum blood pressure is controversial. A number of international guidelines have changed their blood pressure targets to <140/90 mmHg,^{3,12} while others remain at <130/80 mmHg.¹³ Some suggest that low targets such as <130/80 mmHg could be appropriate for people at high risk of CVD, if achievable without undue treatment burden.¹²

Considering these guidelines, the RACGP recommends a blood pressure target of <140/90 mmHg for people with diabetes, with lower targets considered for younger people and those at high risk of stroke, as long as the treatment burden is not high.

For secondary prevention of CVD, the target blood pressure for people with diabetes and microalbuminuria or proteinuria (emergent chronic kidney disease) remains <130/80 mmHg. As always, treatment targets should be individualised and people with diabetes monitored for side effects from the use of medications to achieve lower targets.

Lipid-lowering medication

GPs should consider treatable secondary causes of raised blood lipids before commencing pharmacotherapy.

Statins remain the clear first-line choice when commencing pharmacotherapy.

The results from several systematic reviews are consistent, and suggest that people with diabetes gain at least similar benefits as people without diabetes. The data clearly demonstrate that statin therapy results in a significant decrease in coronary artery disease morbidity and mortality in type 2 diabetes for those at high CVD risk.^{1,14,15} This benefit is in contrast to the contentious effects of improved glycaemic control in CVD risk management.

Statin use for primary prevention of CVD

Statins are indicated for people with diabetes at high absolute risk of CVD, at any cholesterol level.¹

Statin use for secondary prevention

Statin therapy is recommended for all patients with CVD (unless exceptional circumstances apply).

Other lipid-lowering medications

The evidence for using lipid-lowering medications other than statins to decrease the risk of coronary artery disease is still accumulating.

Ezetimibe

Ezetimibe has been studied in the IMPROVE-IT trial in people with diabetes and existing acute coronary syndrome. Compared with a statin alone, ezetimibe combined with a statin showed an absolute risk reduction of 5.5% (40% versus 45.5%) for the composite primary endpoint of cardiovascular death, major coronary events or non-fatal stroke over seven years.¹⁶

Thus, in adults, ezetimibe combined with a statin (simvastatin) in diabetes patients with acute coronary syndrome may provide additional low-density lipoprotein cholesterol (LDL-C) lowering (if >1.8 mmol/L on statin therapy) and CVD risk reduction.

Nicotinic acid, bile-acid resins and fibrates

These agents have been suggested as alternatives for people who cannot tolerate statins.

Nicotinic acid (niacin) has been shown in one trial to reduce CVD outcomes, although the study was done in a cohort of people without diabetes.¹⁷ More recent trials have not confirmed this initial result. The use of nicotinic acid, in particular, as well as gemfibrozil and cholestyramine is limited by a high rate of adverse effects.

The role of fibrates (fenofibrate, gemfibrozil) to decrease CVD is contentious. Fibrates, preferably fenofibrate, should be commenced in addition to a statin or on their own (for those intolerant to statin) when fasting triglycerides are ≥ 2.3 mmol/L, or HDL-C is low.²

Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9)

PCSK9 are injectable lipid-lowering agents, some of which have restricted Therapeutic Goods Administration (TGA) and Pharmaceutical Benefits Scheme (PBS) approval for use in select high-risk patients. Long-term outcome studies on safety are needed. For more information, refer to the websites for the TGA and the PBS.

Antithrombotic therapy

It is not usually recommended that antiplatelet therapy (eg aspirin, clopidogrel) be used in primary prevention of CVD. For secondary prevention, the strong positive effects in the conditions outlined in the '[Recommendations](#)' need to be weighed against individual patient risks.

Glucose-lowering medications (novel non-glycaemic effects)

In populations with existing CVD, cardiovascular outcome trials have been conducted for newly developed diabetes drugs to demonstrate, primarily, cardiovascular safety and various secondary non-glycaemic endpoints. Some trials did include people with multiple risk factors for CVD. The trials were not glycaemic efficacy trials.

Summary of outcomes

Refer to the individual trial designs and outcomes for specific drug effects.

Sodium glucose co-transporter 2 (SGLT2) inhibitors

A 2019 meta-analysis of the cardiovascular outcomes trials showed that SGLT2 inhibitors led to:¹⁸

- 11% reduction in major adverse cardiovascular events, seen only in those with established CVD, but not those without CVD
- 23% reduction in CVD death or hospitalisation for heart failure in those with or without atherosclerotic disease or heart failure.

Future clinical trials are focused on specific non-glycaemic benefits in heart failure (with or without diabetes) and renal outcomes. The exact mechanism of action on CVD and heart failure has not been fully elucidated.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs)

A 2018 meta-analysis showed that GLP-1 RAs led to:¹⁹

- 10% reduction in primary endpoints for major adverse cardiovascular outcomes
- 13% reduction in cardiovascular mortality
- 12% reduction in all-cause mortality.

Non-significant effects were demonstrated on fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, hospital admission for unstable angina, and hospital admission for heart failure.

The exact mechanism of action has not been fully elucidated.

Dipeptidyl peptidase-4 inhibitors (DPP-4i)

Recent meta-analyses for DPP-4i showed:²⁰⁻²²

- safety, but non-significant benefits for cardiovascular outcomes in those with high risk for cardiovascular events or with established CVD
- statistically non-significant 5% increased risk of hospitalisation for heart failure.

Sulfonylureas

Meta-analyses of randomised clinical trials for sulfonylureas have shown:

- no excess cardiovascular risks associated with this class^{23,24}
- lower all-cause and cardiovascular mortality associated with gliclazide and glimepiride compared with glibenclamide.²⁵

References

1. National Vascular Disease Prevention Alliance. Guidelines for the management of absolute cardiovascular disease risk. Melbourne: National Stroke Foundation, 2012.
2. Baker IDI Heart and Diabetes Institute. National evidence-based guideline on secondary prevention of cardiovascular disease in type 2 diabetes (Part of the Guidelines on management of type 2 diabetes). Melbourne: Baker IDI Heart and Diabetes Institute, 2015.
3. NHFA CSANZ Heart Failure Guidelines Working Group. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Guidelines for the prevention, detection and management of heart failure in Australia 2018. *Heart Lung Circ* 2018;27(10):1123–208.
4. National Heart Foundation of Australia. Guideline for the diagnosis and management of hypertension in adults – 2016. Melbourne: National Heart Foundation of Australia, 2016.
5. Stroke Foundation. Clinical guidelines for stroke management. Melbourne: Stroke Foundation, 2019. Available at <https://informme.org.au/en/Guidelines/Clinical-Guidelines-for-Stroke-Management> [Accessed 16 April 2020].
6. Shah AD, Langenberg C, Rapsomaniki E, et al. Type 2 diabetes and incidence of cardiovascular diseases: A cohort study in 1.9 million people. *Lancet Diabetes Endocrinol* 2015;3(2):105–13.
7. Royal Australian College of General Practitioners. Guidelines for preventive activities in general practice. 9th edn. East Melbourne, Vic: RACGP, 2016.
8. Saha S, Carlsson KS, Gerdtham UG, et al. Are lifestyle interventions in primary care cost-effective? – An analysis based on a Markov model, differences-in-differences approach and the Swedish Bjorknas study. *PLoS One* 2013;8(11):e80672.
9. Saha S, Gerdtham UG, Johansson P. Economic evaluation of lifestyle interventions for preventing diabetes and cardiovascular diseases. *Int J Environ Res Public Health* 2010;7:3150–95.
10. Look AHEAD Research Group; Wing RR, Bolin P, Brancati FL, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013;369(2):145–54.
11. ONTARGET Investigators; Yusuf S, Teo K, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;358(15):1547–59.
12. De Boer IH, Bangalore S, Benetos A, et al. Diabetes and hypertension: A position statement by the American Diabetes Association. *Diabetes Care* 2017;40(9):1273–84.
13. Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes* 2018;42(Suppl 1):S1–S325.
14. Koo B. Statin for the primary prevention of cardiovascular disease in patients with diabetes mellitus. *Diabetes Metab J* 2014;38:32–4.
15. Cholesterol Treatment Trialists' (CTT) Collaborators; Kearney PM, Blackwell L, Collins R, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: A meta-analysis. *Lancet* 2008;371(9607):117–25.
16. Giugliano RP, Cannon CP, Blazing MA, et al. Benefit of adding ezetimibe to statin therapy on cardiovascular outcomes and safety in patients with versus without diabetes mellitus. *Circulation* 2018;137(15):1571–82.
17. Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in Coronary Drug Project patients: Long-term benefit with niacin. *J Am Coll Cardiol* 1986;8(6):1245–55.
18. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcome trials. *Lancet* 2019;393(10166):31–39.
19. Bethel MA, Patel RA, Merrill P, et al. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: A meta-analysis. *Lancet Diabetes Endocrinol* 2018;6(2):105–13.

20. Mannucci E, Monami M. Cardiovascular safety of incretin-based therapies in type 2 diabetes: Systematic review of integrated analyses and randomized controlled trials. *Adv Ther* 2017;34:1–40.
21. Liu D, Jin B, Chen W, Yun, P. Dipeptidyl peptidase 4 (DPP-4) inhibitors and cardiovascular outcomes in patients with type 2 diabetes mellitus (T2DM): A systematic review and meta-analysis. *BMC Pharmacol Toxicol* 2019;20(1):15.
22. Nauck M, Meier J, Cavender M, Abd El Aziz M, Drucker DJ. Cardiovascular actions and clinical outcomes with glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. *Circulation* 2017;136(9):849–70.
23. Palmer SC, Mavridis D, Nicolucci A, et al. Comparison of clinical outcomes and adverse events associated with glucose-lowering drugs in patients with type 2 diabetes: A meta-analysis. *JAMA* 2016;316(3):313–24.
24. Varvaki Rados D, Catani Pinto L, Reck Remonti L, Bauermann Leitão C, Gross JL. The association between sulfonylurea use and all-cause and cardiovascular mortality: A meta-analysis with trial sequential analysis of randomized clinical trials. *PLoS Med* 2016;13(4):e1001992.
25. Simpson SH, Lee J, Choi S, Vandermeer B, Abdelmoneim AS, Featherstone TR. Mortality risk among sulfonylureas: A systematic review and network meta-analysis. *Lancet Diabetes Endocrinol* 2015;3(1):43–51.

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