Diabetes and CVD risk in women

Optimising outcomes

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Women with type 2 diabetes are at high risk of cardiovascular disease. Early identification and modification of diabetes and cardiovascular risk factors, and adherence to clinical management guidelines are essential for optimising outcomes.

Type 2 diabetes is a major public health problem, affecting more than 800,000 people in Australia.[1] The Australian Diabetes, Obesity and Lifestyle (AusDiab) study showed that 7% of adults have a known diagnosis of diabetes and up to an additional 7% have undiagnosed diabetes.[2]

Cardiovascular disease is the most common complication affecting patients with type 2 diabetes and is responsible for death in more than 30% of people.[3] Cardiovascular disease is defined as all diseases of the heart and blood vessels including coronary heart disease, stroke, peripheral vascular disease and heart failure, and is the leading cause of death in women, responsible for the death of almost 24,000 women in Australia per year.[3]

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KEY POINTS

- Cardiovascular disease is the most common complication affecting patients with type 2 diabetes and is responsible for death in more than 30% of them.
- The protective effect against cardiovascular disease usually afforded to women is eliminated by the presence of diabetes.
- Women with type 2 diabetes have a much higher relative risk of developing and dying from cardiovascular disease than men with diabetes.
- Many women experience less intensive screening and management of cardiovascular risk factors than men.
- Women at high risk of type 2 diabetes and cardiovascular disease can be identified early by using established screening algorithms such as the Australian type 2 diabetes risk assessment tool (AUSDRISK) and the Australian absolute cardiovascular risk calculator, which are both available as online tools.
- Women with a history of gestational diabetes or polycystic ovary syndrome are at increased risk of type 2 diabetes, and require early identification and modification of metabolic risk factors, regular screening for diabetes and intensive management of cardiovascular risk factors.
- Women with type 2 diabetes require close attention to cardiovascular disease risk stratification and intensive monitoring and management, which can be achieved by adherence to best practice clinical guidelines.

Although type 2 diabetes is a major risk factor for cardiovascular disease in both men and women, this effect is much stronger for women. In the general population, women have a lower risk of cardiovascular disease than men, yet in the presence of type 2 diabetes the premenopausal protection from cardiovascular disease afforded to women is essentially lost.[4,5] Women with type 2 diabetes compared with women without diabetes have a much higher relative risk of developing and dying from cardiovascular disease than men with type 2 diabetes compared with men without diabetes (incident coronary heart disease relative risk for women 2.82 [95% confidence interval, 2.35–3.38] and for men 2.16 [95% confidence interval, 1.82–2.56]).[4,6,7] The risk of stroke has also been shown to be significantly higher in women with diabetes than men with diabetes independent of other risk factors for cardiovascular disease.[8] Furthermore, women with type 1 diabetes have been found to have a 37% higher chance of dying from stroke than men with type 1 diabetes.[9]

Despite this, women with diabetes often experience less intensive screening and management of cardiovascular risk factors than men with diabetes. We explore the possible reasons behind the sex difference in cardiovascular mortality risk between women and men with type 2 diabetes, and discuss strategies for reducing this disparity.

Factors contributing to CVD risk in women with diabetes

Risk factor profile

Although it is well established that the presence of diabetes clearly has a greater impact on the risk of cardiovascular disease in women than in men, the mechanisms behind this are not completely understood. Factors thought to contribute include sex differences in the prevalence and management of cardiovascular risk factors, and possibly a greater physiological effect of diabetes and metabolic risk factors in women than in men.[4,5]

Women with diabetes appear to have more adverse modifiable metabolic risk factors, such as being overweight or obese and having high blood pressure and abnormal lipid profiles, than men with diabetes.[10] At diagnosis of diabetes, women have higher low-density lipoprotein (LDL) cholesterol levels and systolic blood pressure than men.[11]

A prospective study reporting a much higher diabetes-related relative risk of death from coronary heart disease or nonfatal myocardial infarction during follow up demonstrated a heavier burden of obesity, high blood pressure and adverse lipid profile in women than in men with diabetes at study entry.[5] Women with diabetes, compared with women without diabetes, have been reported to have greater central obesity, lower high-density lipoprotein (HDL) cholesterol levels and a larger difference in LDL particle size.[4]

Management factors

Despite this high burden of metabolic risk, many women experience less intensive management of cardiovascular risk factors than men. Women tend to have poorer blood glucose control and despite more severe elevations in blood pressure and lipid levels, are less likely to be prescribed insulin, lipid-lowering therapies, antihypertensive agents and aspirin than men.[4,6]

Many women themselves perceive cardiovascular disease as a men's health problem and under-recognise the role of diabetes, high cholesterol levels and high blood pressure in heart disease.[12] This may explain why women show lower adherence to treatment for diabetes and presents a potential barrier to women engaging in strategies to identify and modify cardiovascular risk.[6,13]

Factors likely to be important contributors to the increased mortality due to coronary heart disease in women with diabetes are differences in hospital presentation and care of women with acute coronary syndromes (ACS). Compared with men with ACS, women are more likely to present late with atypical symptoms, less likely to be cared for by a cardiologist and less likely to have intensive investigations and management such as stress testing, coronary angiography and revascularisation.[13] Furthermore, proven secondary preventive therapies are less frequently prescribed to women after ACS.[13]

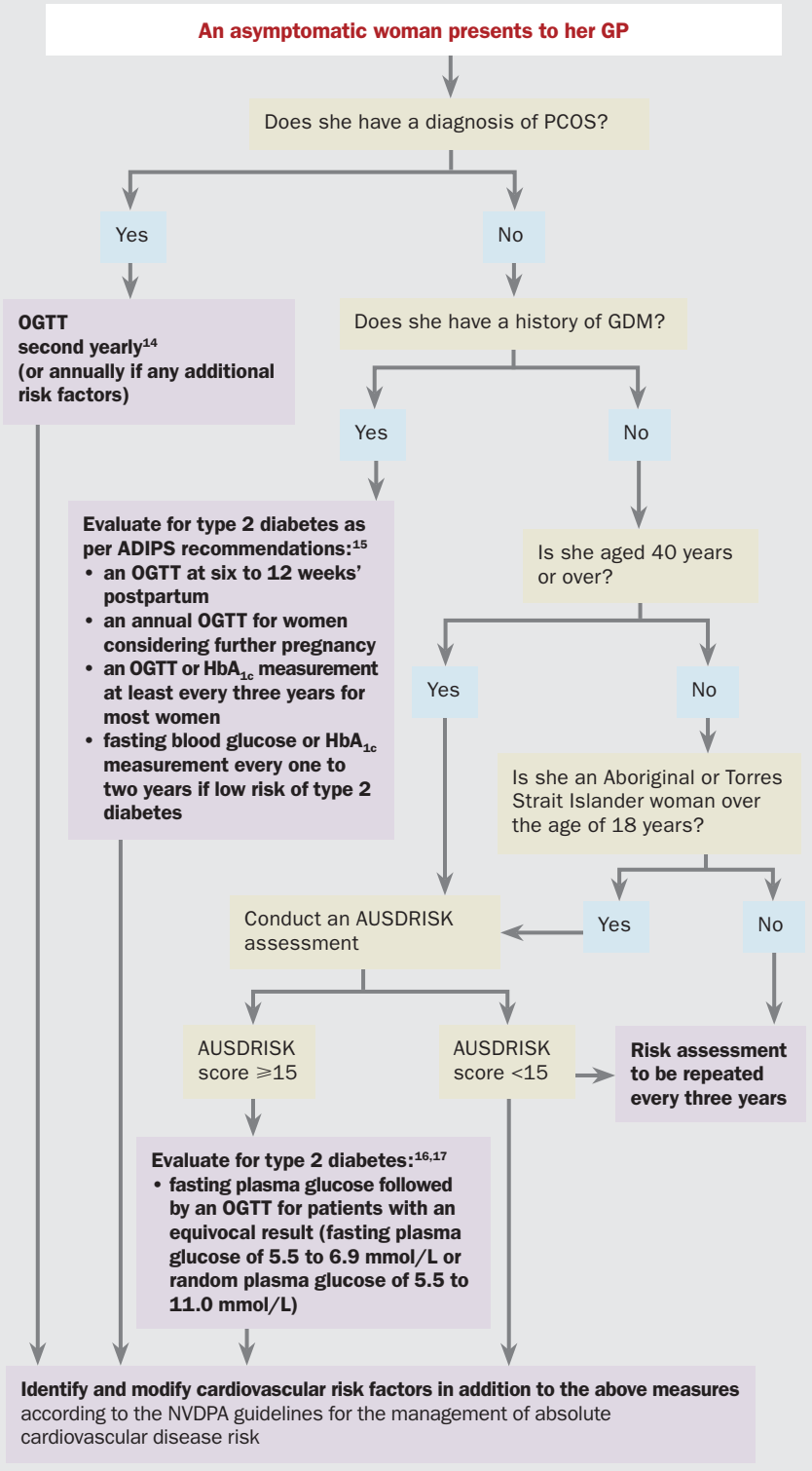
Screening and prevention of type 2 diabetes

GPs play an important role in facilitating early screening for diabetes and metabolic risk factors. This is essential for not only the early detection of diabetes, but also the identification of women at high risk of developing diabetes, metabolic syndrome and cardiovascular disease, in whom the progression to type 2 diabetes may be prevented or delayed. Lifestyle interventions form the basis for prevention strategies, whereas in a few selected obese patients, medications or bariatric surgery may be considered. The flowchart outlines a suggested approach to screening for diabetes, metabolic syndrome and cardiovascular disease in women.[14-17]

Screening for diabetes

All women presenting with symptoms of diabetes or conditions known to be complications of diabetes require evaluation for diabetes. In asymptomatic individuals, the Australian type 2 diabetes risk assessment tool (AUSDRISK) should be used for screening to identify patients at high risk of developing type 2 diabetes, by assessing them for known diabetes risk factors.[16,18] A score of 15 or more indicates a high risk of developing diabetes. AUSDRISK is available as an online tool through the Australian Government Department of Health website (www.health.gov.au).[18] This and other relevant online resources are outlined in Box 1. Completion of the tool is recommended for all adults from age 40 years, or age 18 years in Aboriginal and

A SUGGESTED APPROACH TO SCREENING FOR DIABETES, THE METABOLIC SYNDROME AND CARDIOVASCULAR DISEASE IN WOMEN



Abbreviations: ADIPS = Australasian Diabetes in Pregnancy Society; AUSDRISK = Australian type 2 diabetes risk assessment tool; GDM = gestational diabetes; HbA_{1c} = glycosylated haemoglobin; NVDPA = National Vascular Disease Prevention Alliance; OGTT = oral glucose tolerance test; PCOS = polycystic ovary syndrome.

Torres Strait Islander people, with repeat evaluation every three years.[16] High-risk individuals require evaluation for type 2 diabetes and measures to modify risk factors, as discussed below. The NHMRC also recommends evaluation for diabetes in those with additional risk factors for diabetes, including women with a history of gestational diabetes, polycystic ovary syndrome (PCOS) and the metabolic syndrome (Box 2).[16]

Women with gestational diabetes have a sevenfold increased risk of developing type 2 diabetes.[19] Women with gestational diabetes should be screened with an oral glucose tolerance test (OGTT) at six to 12 weeks' postpartum, unless contraindicated.[14] An annual OGTT is suggested for women considering further pregnancy.[14] The Australasian Diabetes in Pregnancy Society (ADIPS) recommends postpartum screening for the development of type 2 diabetes based on the perceived risk to the individual patient; most women with a history of gestational diabetes require an OGTT or glycosylated haemoglobin (HbA_{1c}) measurement at least every three years.[14,20] For women who have a history of gestational diabetes but are otherwise considered to be at low risk of type 2 diabetes, measurement of fasting glucose or HbA_{1c} levels every one to two years is considered sufficient.[14]

In women with PCOS, the coexistence of insulin resistance with obesity and inactivity increases the likelihood of developing gestational diabetes, type 2 diabetes and subsequent cardiovascular disease across the lifetime (Box 3).[21,22] For women with a diagnosis of PCOS, the Australian *Evidence-Based Guideline for the Assessment and Management of Polycystic Ovary Syndrome* recommends an OGTT every second year, or annually in those with an additional risk factor for developing type 2 diabetes.[15]

Women at high risk of diabetes are now eligible for reimbursement of the cost of HbA_{1c} quantification for the diagnosis of diabetes.[23]

1. ONLINE RESOURCES FOR DIABETES SCREENING AND MANAGEMENT

- The Australian type 2 diabetes risk assessment tool (AUSDRISK) – http://www.health.gov.au/internet/main/publishing.nsf/Content/diabetesRiskAssessmentTool
- The National Vascular Disease Prevention Alliance (NVDPA) guidelines for the management of absolute cardiovascular disease risk – http://strokefoundation.com.au/site/media/AbsoluteCVD_GL_webready.pdf
- NVDPA Australian absolute cardiovascular risk calculator – http://www.cvdcheck.org.au
- The Australian Diabetes Society (ADS) blood glucose management algorithm for type 2 diabetes – https://diabetessociety.com.au/position-statements.asp
- The Australian Diabetes in Pregnancy Society (ADIPS) consensus guidelines for the testing and diagnosis of hyperglycaemia in pregnancy in Australia and New Zealand – http://adips.org/downloads/2014ADIPSGDMGuidelinesV18.11.2014_000.pdf

2. RISK FACTORS FOR TYPE 2 DIABETES IDENTIFIED BY THE NHMRC[16]

Nonmodifiable risk factors

- Age
- Genetics/family history
- Male sex
- Ethnic group (Southern European, Northern African, Middle Eastern, Pacific Islander, South Asian)
- Aboriginal and Torres Strait Islander people

Modifiable risk factors

- Overweight and obesity
- Physical inactivity
- Dietary intake
- Smoking
- Psychological stress

Others

- Gestational diabetes
- Polycystic ovary syndrome
- Metabolic syndrome

Prevention of diabetes and the metabolic syndrome

Preventing progression to diabetes and the metabolic syndrome in patients at high risk of diabetes begins with education and involvement in a lifestyle-modification program. Patients may require intensive and sustained support from a multidisciplinary healthcare team and their family to achieve changes to their diet and physical activity levels, and to reach weight loss targets.[24] Referral to a dietitian and physical activity program is recommended.

Additionally, in women with gestational diabetes, efforts to prevent type 2 diabetes can begin early with avoidance of excess weight gain in pregnancy and education on the benefits of achieving a healthy weight postpartum.[25] Making the diagnosis of PCOS or gestational diabetes offers an opportunity to identify women who will benefit from achieving or maintaining a healthy weight. It also allows for the identification and management of other modifiable metabolic risk factors.

CVD risk estimation and management

In women with type 2 diabetes, regular assessment of the risk of cardiovascular disease, assistance with lifestyle modification, achieving glycaemic control and early detection of cardiovascular disease, when it does occur, is required within general practice.

CVD risk assessment and stratification

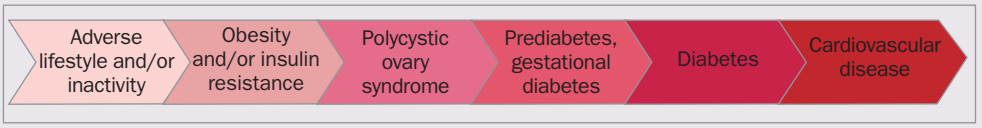
Routine assessment of cardiovascular disease risk is essential in women with a diagnosis of diabetes. High cardiovascular disease risk can be clinically determined based on significant cardiovascular disease risk factors, including:[26]

- age over 60 years
- microalbuminuria
- moderate or severe chronic kidney disease (estimated glomerular filtration rate <45 mL/min/1.73 m^2)
- previous diagnosis of familial hypercholesterolaemia
- marked hypertension (systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg)
- total cholesterol above 7.5 mmol/L.

For adults with diabetes who do not meet these clinically determined criteria for high risk and do not have a history of cardiovascular disease, the National Vascular Disease Prevention Alliance (NVDPA) guidelines

3. COEXISTING LIFESTYLE-RELATED DISEASES AND THE PROGRESSION TO DIABETES AND CARDIOVASCULAR DISEASE*

The proposed continuum of lifestyle-related diseases from physical inactivity and/or obesity through the progression of insulin resistance to polycystic ovary syndrome and gestational diabetes (in women), prediabetes, diabetes and potentially cardiovascular disease.



* Reproduced with permission from Teede HJ, et al. *Trends Endocrinol Metab* 2007; 18: 273-279.[21]

for the management of absolute cardiovascular disease risk recommend estimation of absolute cardiovascular disease risk using the Framingham Risk Equation.[26] This equation can be used to predict the risk of a cardiovascular event over the next five years. The NVDPA Australian absolute cardiovascular risk calculator is based on the equation and is available online (Box 1).[27]

Lifestyle modification

Lifestyle modification plays a fundamental role in the management of patients with diabetes, to achieve glycaemic control and modify cardiovascular risk. All

TABLE 1. SUMMARY OF THE NATIONAL VASCULAR DISEASE PREVENTION ALLIANCE (NVDPA) GUIDELINES FOR THE MANAGEMENT OF ABSOLUTE CARDIOVASCULAR DISEASE RISK RECOMMENDATIONS*

CVD risk	Lifestyle	Pharmacotherapy	Targets	Monitoring
High risk Clinically determined or calculated using FRE as >15% absolute risk of CVD events over 5 years	• Frequent and sustained specific advice and support regarding diet and physical activity • Appropriate advice, support and pharmacotherapy for smoking cessation • Advice given simultaneously with BP and lipid-lowering drug treatment	• Treat simultaneously with lipid lowering and BP lowering unless contraindicated or clinically inappropriate • Aspirin not routinely recommended • Consider withdrawal of therapy for people who make profound lifestyle changes	**BP** • ⩽140/90 mmHg in general or people with chronic kidney disease • ⩽130/80 mmHg in all people with diabetes • ⩽130/80 mmHg if micro or macroalbuminuria (UACR >2.5 mg/mmol in men and >3.5 mg/mmol in women) **Lipids** • total cholesterol <4.0 mmol/L • HDL-cholesterol ⩾1.0 mmol/L • LDL-cholesterol <2.0 mmol/L • Non-HDL-cholesterol <2.5 mmol/L • Triglycerides <2.0 mmol/L **Lifestyle** • Smoking cessation (if smoker) • Consume diet rich in vegetables and fruit, low in salt and low in saturated and trans fats • At least 30 minutes moderate intensity physical activity on most or preferably every day of the week • Limit alcohol intake	• Adjust medication as required • Review of absolute risk according to clinical context
Moderate risk Calculated using FRE as 10 to 15% absolute risk of CVD events over 5 years	• Appropriate, specific advice and support regarding diet and physical activity • Appropriate advice, support and pharmacotherapy for smoking cessation • Lifestyle advice given in preference to drug therapy	• Not routinely recommended • Consider BP lowering and/or lipid lowering in addition to lifestyle advice if 3 to 6 months of lifestyle intervention does not reduce risk or: – BP persistently ⩾160/100 mmHg – family history of premature CVD – specific population where the FRE underestimates risk; e.g. Aboriginal and Torres Strait Islander Australians, South Asian, Maori and Pacific Islander, Middle Eastern • Consider withdrawal of therapy for people who make profound lifestyle changes		• Adjust medication as required • Review absolute risk every 6 to 12 months
Low risk Calculated using FRE as <10% absolute risk of CVD events over 5 years	• Brief, general lifestyle advice regarding diet and physical activity • Appropriate advice, support and pharmacotherapy for smoking cessation	• Not routinely recommended • Consider BP-lowering therapy in addition to specific lifestyle advice if BP persistently ⩾160/100 mmHg • Consider withdrawal of therapy for people who make profound lifestyle changes		• Adjust medication as required • Review absolute risk every 2 years • Blood test results within 5 years can be used

Abbreviations: BP = blood pressure; CVD = cardiovascular disease; FRE = Framingham Risk Equation; UACR = urinary albumin:creatinine ratio.
* Reproduced with permission from the *NVDPA Guidelines for the Management of Absolute Cardiovascular Disease Risk*, 2012.[26]

women who are overweight or obese (body mass index ⩾25 kg/m^2) should be recommended to lose weight, aiming for 5 to 7% loss of total bodyweight. The NVDPA guidelines recommend patients aim for 30 minutes of physical activity at moderate intensity on most days of the week;[26] however, more recently the NHMRC suggested that 45 to 60 minutes is required.[28] Even patients with a history of ischaemic heart disease can participate in safe exercise programs to increase their levels of physical activity.[29] For women who smoke, smoking cessation should be strongly advised and supported.

A summary of the NVDPA recommendations for the management of patients according to cardiovascular disease risk stratification is given in Table 1.[26]

Treatment of cardiovascular risk factors

In patients with diabetes, an ACE inhibitor or angiotensin-receptor blocker should be used to lower blood pressure, if not contraindicated. A calcium channel blocker or thiazide diuretic can be added if a second agent is required.[26]

Statins should be used as first-line lipid-lowering therapy to achieve the lipid targets outlined in the NVDPA guidelines (Table 1). The statin should be increased to maximal tolerated dose if LDL-cholesterol levels are not adequately lowered.[26] The addition of ezetimibe, bile acid-binding resin or nicotinic acid should follow if LDL-cholesterol levels remain above target on the maximal statin dose.[26]

Antiplatelet agents are not routinely recommended in patients with no history of cardiovascular disease, regardless of risk category.[26]

Achieving glycaemic targets

Achieving glycaemic control is known to be important in reducing microvascular complications in people with type 2 diabetes and may also reduce the incidence of myocardial infarction.[30] The effects on the incidence of stroke and all-cause mortality are less well defined.[30]

For most women with diabetes, the Australian Diabetes Society recommends a general HbA_{1c} target of 53 mmol/mol (7%) or less. However, this should be individualised, with particular caution exercised when treating people who are older, have existing cardiovascular disease or previous episodes of severe hypoglycaemia (Table 2).[30,31]

In 2014, the Australian Diabetes Society released a blood glucose management algorithm for patients with type 2 diabetes, which details the recommended approach to the selection of glucose-lowering therapies to achieve glycaemic targets.[30] The algorithm, available on the Australian Diabetes Society website (https://diabetessociety.com.au/position-statements.asp), recommends the use of metformin as first-line therapy, with the addition of a sulfonylurea when a second-line agent is required to achieve glycaemic targets. Dual therapy with

metformin and a dipeptidyl peptidase-4 (DPP-4) inhibitor or sodium-glucose cotransporter 2 (SGLT2) inhibitor is advised when a sulfonylurea is contraindicated or not tolerated. When glycaemic control remains inadequate the options include the use of a glucagon-like peptide-1 receptor agonist (GLP1-RA), addition of insulin or use of triple oral therapy.[30] Women with type 2 diabetes should be managed according to this algorithm where possible, in conjunction with diet, exercise and diabetes education.

TABLE 2. RECOMMENDED HbA_{1c} TARGETS IN ADULTS WITH TYPE 2 DIABETES[31]

Patient characteristics	HbA_{1c} target	
	%	mmol/mol
General target	<7.0	53
Specific clinical situations		
Diabetes of short duration and no clinical cardiovascular disease		
• Requiring lifestyle modification and/or metformin	⩽6.0*	42
• Requiring any antidiabetic agents other than insulin	⩽6.5*	48
• Requiring insulin	⩽7.0*	53
Pregnancy or planning pregnancy	⩽6.0*	42
Diabetes of longer duration or clinical cardiovascular disease (any therapy)	⩽7.0*	53
Recurrent severe hypoglycaemia or hypoglycaemia unawareness (any therapy)	⩽8.0*	64
Patients with major comorbidities likely to limit life expectancy	Symptomatic therapy of hyperglycaemia	
Special considerations		
Older people	Individualised†	

*Achieving HbA_{1c} target should be measured against individual risk of hypoglycaemia.
†Glycaemic targets should be individualised in older people, based on frailty, life expectancy and cognitive impairment; target may be symptom control or HbA_{1c} ⩽8% (64 mmol/mol).[30]

Management of cardiovascular disease in women with diabetes

Vigilance is required in screening women for symptoms of cardiovascular disease during clinical encounters and identifying symptoms, which may be atypical, when they do occur. In respect to ACS, compared with men, women are less likely to experience chest pain and more frequently report associated symptoms, including nausea, dizziness, weakness, fatigue, jaw or back pain, or dyspnoea.[4] Additionally, women tend to present late with ACS, highlighting the need to educate women on their cardiovascular disease risk, symptoms of ACS and the importance of seeking early medical assistance. Menopause can be an excellent opportunity to intervene in terms of risk perception and patient interest in self-care.

The reasons behind sex discrepancies in evidence-based quality care of women with ACS are unclear. Having an awareness of the tendency to undertreat women with cardiovascular disease both acutely and with secondary prevention may assist practitioners in being attentive to clinical practice guidelines for the management of cardiovascular disease in women with diabetes.

Conclusion

Multiple factors contribute to the greater impact of diabetes on the risk of cardiovascular disease in women than in men. Early screening for diabetes risk, lifestyle modification and achieving weight loss are the cornerstones of managing women at risk of diabetes and cardiovascular disease. For women with a diagnosis of type 2 diabetes, intensive monitoring and management of diabetes and cardiovascular risk factors can be assisted by adherence to best practice clinical guidelines such as the Australian Diabetes Society blood glucose management algorithm and the NVDPA guidelines for the management of absolute cardiovascular disease risk. MT

References

A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

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