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NEED TO KNOW

- Ischaemic heart disease (IHD) is a leading cause of death in Australian women; it is not only a 'male' disease.
- There are several sex-based disparities in outcomes and quality of care in women with IHD.
- Cardiovascular disease (CVD) risk factors for women can be classified as traditional, non-traditional and specific to women.
- There are gender disparities in both traditional and non-traditional risk factors such as depression, socioeconomic status and environmental factors.
- Women specific risk factors include adverse pregnancy outcomes, and non-obstetric factors including premature menopause, polycystic ovarian syndrome and endometriosis.
- Autoimmune disorders (SLE and rheumatoid arthritis) are more prevalent in women and associated with increased cardiovascular risk.
- Breast cancer treatment has adverse cardiovascular effects.
- Reducing cardiovascular risk in women involves identifying and recognising those with all these CVD risk factors; take a pregnancy and gynaecological history; screen for traditional risk factors; aggressively manage risk factors and regularly follow-up.

Cardiovascular risk in women

Dr Fiona Foo
General and interventional cardiologist, Sydney Cardiology Group and MQ Health Cardiology, Macquarie University Hospital, Sydney Adventist Hospital and Norwest Private Hospital, Sydney, NSW.

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BACKGROUND

ISCHAEMIC heart disease (IHD) is a leading cause of death in Australian women (second to dementia), accounting for 9.2% of deaths, 2.3 times as many as breast cancer.[1] IHD claims an average of 20 female lives every day.[1] Over the past 10 years 94,000 Australian woman died from coronary heart disease (CHD).[1] In 2020, of 57,275 MIs, 19,181 were in women.[2] In 2019 there were 7101 deaths from MI, 3168 in women.[1] Regardless of age, women are more likely to die within one year of their first MI (26% vs 19%).[3]

There is under recognition and lack of awareness of cardiovascular disease (CVD) in women by both healthcare professionals and women.[4] Around 20% of CHD events in women occur in the absence of conventional risk factors, and current tools are inadequate at assessing risk in young women.[5,6] Sex-specific cardiovascular risk factors, such as adverse pregnancy outcomes (APOs), can be utilised.[7] An understanding of women specific risk factors is imperative to disease prevention.[8]

This How to Treat focuses on risk factors for atherosclerotic CVD (ASCVD), in particular CHD or coronary artery disease (CAD) and IHD. It aims to ensure GPs can appropriately assess CVD risk in women and implement risk management strategies.

OUTCOME DISPARITIES

THERE are several sex-based disparities in outcome and quality of care in patients with IHD (see table 1).[9] In Australia, women with ST elevation MI (STEMI) experience excess delays (patient, pre-hospital system and hospital) and are less likely to receive invasive management, revascularisation, or preventive medication at discharge.[10,11] Women have less cholesterol screening, fewer lipid lowering therapies, fewer cardiac rehabilitation referrals and are less often prescribed antiplatelet therapy and beta-blockers for secondary prevention.[12]

RISK FACTORS

ASCVD risk factors can be thought of as traditional, non-traditional and those disproportionately affecting women/women specific (see box 1).

Traditional risk factors

Traditional risk factors for ASCVD are well known, however there are gender disparities (see table 2).

Women specific risk factors

These are listed in box 1 and detailed below.

ADVERSE PREGNANCY OUTCOMES

Pregnancy is considered a physiological 'stress test' because it requires the cardiovascular system to work at 30-50% extra load.[58] Most women can cope with this demand; however, up to 30% of pregnancies have an adverse pregnancy outcome (APO, see table 3), which is associated with an increased risk of future CVD.[59-61] The more severe the APO or the more pregnancies complicated by an APO, the greater the CVD risk.[62] Abnormal endothelial function and placental dysfunction may be the common mechanism leading to increased cardiometabolic risk.[63]

Hypertensive disorders of pregnancy

Hypertensive disorders of pregnancy (HDP, see box 2) are the most common pregnancy complication and include gestational hypertension (GH), pre-eclampsia, chronic hypertension, pre-eclampsia superimposed on chronic hypertension and eclampsia. Up to 30,000 Australian women develop hypertension in pregnancy each year.[65] All HDP are associated with the development of both future hypertension and other CVD risk factors such as diabetes and hyperlipidaemia as well as future CVD (IHD, CAD, stroke, renal disease, heart failure and valvular heart disease).[66-73]

Preterm delivery

Delivery before 37 weeks' gestation affects about 11% of pregnancies (worldwide) and can be ▸

spontaneous or idiopathic.[86] Elective or iatrogenic preterm delivery (PTD) occurs secondary to a medical or obstetric indication, commonly pre-eclampsia or small for gestational age (SGA). PTD increases future risk of CVD, future maternal cardiovascular events, CVD death, IHD, CHD, CHD death and stroke.[87,88] Risk of CVD is further increased with delivery before 32 weeks and recurrent PTD.[81,89,90]

Small for gestational age

SGA is defined as smaller in size than normal for gestational age/fetal sex or weight below the 10th percentile for the gestational age at delivery. Delivery of an SGA infant is associated with an increased risk of maternal CVD, which increases with moderate and again with extreme SGA infants.[91-95] The maternal risk increases with each SGA infant delivered.[93,95] Women with prior intrauterine growth restriction (IUGR) are at increased risk for hyperlipidaemia, hypertriglyceridaemia and insulin resistance.[96]

CVD RISK, PRE-PREGNANCY RISK FACTORS, AND THE COMBINATION OF PREGNANCY COMPLICATIONS

Pre-pregnancy hypertension increases the risk of pre-eclampsia, while pre-pregnancy overweight/obesity and diabetes increase the risk of GH. The combination of SGA or PTD with HDP further increases the risk of CVD (including hypertension, CAD, heart failure, stroke and CVD mortality). Multiple pregnancy complications and the severity of complications potentiates the risk.[97]

Gestational diabetes

Gestational diabetes (GDM, newly diagnosed diabetes beyond the first trimester) affected around one in six Australian females aged 15-49 who gave birth in hospital in 2017-2018 (16.1% or 43,100 women).[98] The incidence of GDM increased with age, peaking at 31% for females aged 45-49.[98,99] GDM increases the risks of CHD and composite CVD, of CVD in those who subsequently develop type 2 diabetes and of developing IHD/CAD.[99-102]

GDM increases the risk of developing type 2 diabetes, with one third of women developing this 3-5 years post-delivery and nearly 70% more than 10 years postpartum.[101,103,104] There is also an increased risk of stroke, hypertension, dyslipidaemia and atherosclerosis.[101,105-107]

Women with GDM have two times higher the risk of future cardiovascular events. The rates of incident type 2 diabetes did not affect this risk suggesting an independent association between GDM and future CVD risk.[108]

The risks of having both GDM and an HDP are cumulative, with a significantly increased risk of type 2 diabetes, hypertension and CVD mortality than either GDM or HDP alone.[109]

Miscarriage and stillbirth

Most miscarriages (pregnancy loss before 24 weeks' gestation) occur in the first trimester and affect 12-24% of pregnancies.[110,111] Recurrent miscarriage (loss of three or more consecutive pregnancies) affects 1% of couples trying to conceive.[112] Women with a history of stillbirth and miscarriage have an increased risk of CVD, MI, hypertension and stroke.[113-116] Recurrent miscarriage is associated with an even greater risk.[114,115] A history of miscarriage/stillbirth increased the risk of CHD but not stroke, with the risk greater in women with multiple miscarriages/stillbirths.[117]

Table 1. Sex-based disparities in outcome and quality of care

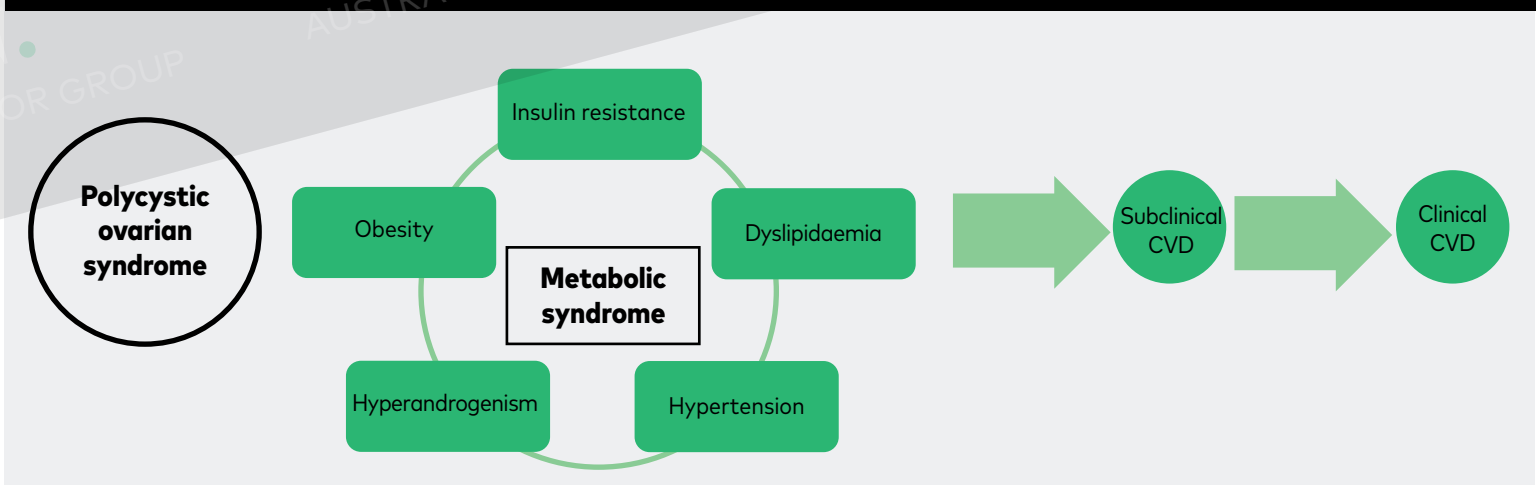
Factors	Sex-specific outcomes
Diagnostic testing	Less than one in 10 women with angina and abnormal stress test had any change in pharmacotherapy or referral for diagnostic angiography[13]
Delay in reperfusion	Women with STEMI had longer median first medical contact to device times and longer pre-hospital delay from symptom onset to hospital presentation compared with men[14,15] Young women more likely to exceed door to needle time guidelines for PCI during STEMI[16]
Fewer revascularisations	Women are less likely to: • Undergo revascularisation after STEMI and NSTEMI[16,17] • Be referred for surgical revascularisation, particularly young women[17,18] • Undergo coronary angiography and PCI if they have stable IHD/angina[19]
Less pharmacotherapy	Women are less likely to achieve guideline-directed secondary prevention targets for lipids, glucose, physical activity or BMI: • Primary prevention: women are less likely to have IHD risk factors measured, and those aged 35-54 are 37% less likely to be prescribed guideline recommended medications[20] • ACS: women are less likely to receive aspirin, ACE inhibitors and statins on discharge[21] • Stable IHD: women report a significantly lower use of statin and aspirin therapy[19]
Morbidity after ACS	ACS: • Women with acute MI had 26% higher one-year rate of rehospitalisation[22,23] • Women with NSTEMIs had higher in-hospital risk of recurrent MI and heart failure[24] • Young women with acute MI experienced more angina and depression, worse quality of life (QoL) and were less likely to return to work within 12 months after MI[23] Stable IHD: • Women with suspected angina but angiographically normal vessels had more hospitalisations and repeat catheterisations for chest pain or ACS; and experienced a decreased QoL[25] • More women than men with confirmed CAD reported recurrent angina[19]
Mortality	ACS: • Women with STEMI had higher in-hospital mortality compared with men (10.2% vs 5.5%)[26] • Women with ACS had higher in-hospital mortality after coronary angiography[27] • Women under 55 had a twofold higher post-infarct in-hospital and one year mortality[28] Stable IHD: • Women with chest pain had higher in-hospital mortality at the time of angiography and higher one-year mortality[27,29] • Women with angiographic CAD had a twofold higher risk of one year death[19]

ACS=acute coronary syndrome, PCI=percutaneous coronary intervention, STEMI=ST-elevation MI, NSTEMI=non-ST-elevation MI

Box 1. Risk factors for ASCVD

- Affecting men and women:
  - Traditional:
    - Hypertension.
    - Hyperlipidaemia.
    - Diabetes.
    - Smoking.
    - Obesity.
    - Physical inactivity.
    - Age.
    - Family history.
  - Non-traditional:
    - Depression.
    - Psychosocial stress.
    - Autoimmune disorders.
    - Income/socioeconomic status.
    - Environment.
- Affecting women:
  - APOs (HDP, gestational diabetes, small for gestational age, preterm delivery, high parity, miscarriage).
  - Menopause (premature menopause, short reproductive lifespan, early menarche, menopause replacement therapy).
  - Endometriosis.
  - Polycystic ovarian syndrome.
  - Breast cancer treatment.
  - Autoimmune/inflammatory disorders (disproportionately affect women).

Figure 1. Metabolic syndrome and CVD



Adapted from Osibogun O et al 2019[128]

Parity

Parity is associated with maternal ASCVD in a J-shaped curve with the greatest relative risk reduction in CVD mortality in women with four pregnancies, with each subsequent pregnancy thereafter conferring an increased risk of developing CVD.[118] Grand multiparity (five or more births) is associated with increased risk of CVD and MI compared with two live births; part of the increase seems to be mediated by weight gain and potentially a higher likelihood of type 2 diabetes mellitus.[119-121] Multiparity is associated with diastolic dysfunction or heart failure with preserved ejection fraction (HFpEF).[122-125]

NON PREGNANCY RELATED RISK FACTORS

Polycystic ovarian syndrome

Polycystic ovarian syndrome (PCOS), an endocrine disorder, affects 4-8% of woman of reproductive age.[126] It commonly causes infertility, and is characterised by a combination of polycystic ovaries, ovulatory dysfunction (oligo- or amenorrhoea), hyperandrogenism (for example, hirsutism and acne) and insulin resistance.[127] The central pathogenic factor is insulin resistance leading to several cardiometabolic abnormalities and putting women at increased CVD risk (see figure 1).[128] PCOS is associated with an increased prevalence of traditional cardiovascular risk factors such as impaired glucose tolerance (IGT), metabolic syndrome and dyslipidaemia, including BMI matched studies.[129-131] It also confers an increase in diabetes, which increases with obesity, but also occurs in lean women.[132] A meta-analysis found patients with PCOS had a higher risk of CVD and CHD.[133,134] The combination of PCOS, diabetes, hypertension and hyperlipidaemia increased the relative risk of CAD more than 21-fold.[135]

Women with a history of stillbirth and miscarriage have an increased risk of CVD, MI, hypertension and stroke.

Endometriosis

This affects up to 10% of women of reproductive age.[136] Young women with endometriosis and possibly older women with a history of endometriosis may be at higher risk of CVD, particularly if early menopause is induced.[137] Endometriosis has been associated with an increased risk of hypertension, hyperlipidaemia, MI, angina and coronary artery bypass graft/stent.[138,139] Endometriosis and ASCVD are diseases of inflammation; this leads to initiation and maintenance of vascular injury and development/progression of atherosclerosis.[137,140]

Premature menopause

CVD risk increases after menopause, due in part to the physiological response to oestrogen withdrawal; this includes higher blood pressure, abnormal lipids, reduced glucose tolerance, changes in body fat distribution, endothelial dysfunction and vascular inflammation.[141]

The usual age of menopause is 51.[142] Premature ovarian failure (POF) and early onset menopause (characterised by loss of ovarian function before age 40-45, cessation of menstruation, hypergonadotropism and hypoestrogenism) are associated with an increased incident CVD and CVD mortality.[143-145]

Premature menopause (age under 40) is a 'risk enhancer' in primary prevention guidelines for CVD, and has been associated with increased CVD, CAD and CVD mortality.[144,146-148] A 2019 pooled analysis reported that women with premature and early menopause (age 40-44) had a substantially increased risk of a non-fatal CVD event (including CHD and stroke),

Table 2. Gender disparities in traditional ASCVD risk factors

Risk factor	Sex-based differences
Diabetes mellitus	• Women with diabetes are more likely to develop and die from CVD than their male counterparts[30,31] • Diabetes is a more potent risk factor for an MI in women[32,33] • Incidence of CAD is greater in women with diabetes[34] • Women with type 1 diabetes onset before age 10 have around a 60 times increased risk of CAD and around a 90 times increased risk of MI[35]
Hypertension	• Hypertension is more prevalent in women aged over 60, and only 29% of these have adequate blood pressure control[36] • Hypertension is a more potent risk factor for MI in women[32,37] • For every 10mmHg increase in systolic blood pressure, women have a 10% greater CVD risk compared with men but there is no difference in CVD mortality[38] • More rapid increase in progressive blood pressure elevation in women starting from age 30-40[39] • Women have less optimisation of their blood pressure[40] • Women more often develop hypertension mediated organ damage and report more drug related side effects[41,42]
Dyslipidaemia	• Elevated cholesterol is a major risk factor for MI in women[32] • Post-menopausal increase in TG, LDL, decrease in HDL[43] • Women are less likely to achieve lipid targets[44]
Obesity	• Obesity is more common in women, particularly post-menopause[45] • Greater excess risk of CVD[46] • Obesity is a major modifiable risk factor for hypertension and is associated with a greater increase in systolic blood pressure in women than men[47]
Physical inactivity	• Women are more physically inactive[48,49] • Women's participation in the recommended amount of physical activity declines with age[48]
Smoking	• Tobacco use is a more potent risk factor for women[50] • Smoking is associated with half of all cardiovascular events in women, and triples the risk of an MI[51] • Tobacco smoking and use of e-cigarettes is increasing in young women globally
Family history (MI or sudden death in father or male first-degree relatives under 55; or under 65 in mother or first-degree female relatives)	• Family history of premature atherosclerosis confers a twofold higher risk of IHD in women[9] • Family history of premature MI doubles the risk of a cardiac event in men and increases the risk in women by around 70%[52] • Maternal history of MI before 60 is the strongest predictor of CVD incidence in those with a family history of MI[53]
Metabolic syndrome (clustering of metabolic risk factors, obesity, hypertension, impaired glucose regulation, dyslipidaemia)	• Present in 20-30% of middle-aged women, with a marked increase after meno-pause[54] • Associated with increased cardiovascular morbidity and mortality[55] • Subclinical and clinical CVD is higher in women with metabolic syndrome[56]
Chronic kidney disease	• A GFR reduction of 10ml/min/1.73m^2 is associated with a 5% increased risk of ASCVD (in both men and women)[57]

Box 2. Hypertensive disorders of pregnancy

- **Gestational hypertension**
  - This is associated with increased risk of chronic hypertension, IHD, MI, MI death, heart failure, stroke, kidney disease and diabetes.[70,72]
  - For women with GH, the relative risk of CVD was 1.8, CAD was 1.7 and stroke was 1.3, compared with women without GH.[74]
  - The increased risk of chronic hypertension is high immediately after pregnancy, with the risk remaining, albeit lower, after 20 years; the risk is higher for first time older mothers.[67]
- **Pre-eclampsia**
  - Pre-eclampsia is the onset of hypertension (above 140/90mmHg) and proteinuria (0.3g/24 hours) after 20 weeks' gestation.
  - There may be renal, haematological, hepatic and neurological dysfunction.
  - It is most common in first pregnancy and abates with delivery of the placenta.
  - Left untreated, pre-eclampsia progresses to eclampsia, characterised by generalised seizures.
  - Pathophysiologic features in common with atherosclerosis include endothelial dysfunction, activation of the coagulation cascade, insulin resistance and lipid abnormalities (increase in LDL, TG, decrease in HDL).
  - Risks associated with pre-eclampsia include:
    - Increased risk of hypertension.[61,70]
    - Increased risk of IHD, stroke, venous thromboembolic events over the 5-10 years after pregnancy.[61,70]
    - Increased coronary artery calcium (CAC) and coronary atherosclerotic plaques on CT coronary angiogram.[75,76]
    - Increased TG and decreased HDL.
    - Increased risk of diabetes.[77,78]
    - Increased risk of microalbuminuria and renal dysfunction.[70,79,80]
    - Increase in CAD, stroke, heart failure and CVD mortality.[81]
  - The CVD risk is increased with recurrent, earlier onset and more severe pre-eclampsia; and with an additional complication such as SGA/PTD:[82,83]
    - Recurrent pre-eclampsia doubles the risk of atherosclerosis (compared with non-recurrent).[82]
    - The risk of a major coronary event was double with pre-eclampsia alone; increased four times with pre-eclampsia and PTD or SGA; and increased six times with pre-eclampsia plus PTD plus SGA.[84]
    - The CHAMPS (Cardiovascular Health after Maternal Placental Syndromes) study found maternal placental syndromes (pre-eclampsia, gestational hypertension, placental abruption, and placental infarction) doubled the risk of premature CVD, the risk was more than three to four times with concomitant fetal growth restriction or intrauterine fetal death.[85]

Table 3. Adverse pregnancy outcomes

Condition	Detail	Definition
Hypertensive disorders of pregnancy	Gestational hypertension	New-onset hypertension (systolic blood pressure more than 140mmHg or diastolic blood pressure more than 90mmHg) after 20 weeks' gestation
	Chronic (pre-existing) hypertension	Hypertension present prior to 20 weeks gestation
	Pre-eclampsia	New-onset hypertension (systolic blood pressure more than 140mmHg or diastolic blood pressure more than 90mmHg) after 20 weeks' gestation with proteinuria or end-organ dysfunction
	Eclampsia	New onset of grand mal seizure activity and/or unexplained coma in a woman with severe pre-eclampsia
Gestational diabetes mellitus		Glucose intolerance with onset or first recognition during pregnancy
Preterm delivery	Preterm birth	Delivery before 37 weeks' gestation
	Early preterm birth	Delivery before 34 weeks' gestation
Intrauterine growth restriction (IUGR) or small for gestational age (SGA)		Fetal birth weight less than expected for gestational age, less than 10th percentile
Pregnancy loss		Miscarriage or stillbirth
High Parity	Grand multiparity	More than five births
Placental abruption		The placenta partly or completely separates from the inner wall of the uterus before delivery

Adapted from Cho L et al 2020[64]

compared with women with menopause at age 50-51.[149] There was a significantly reduced risk of CVD following menopause after age 51. Similarly, the UK Biobank study found premature menopause was associated with an increased risk of CVD.[150]

Premature menopause (age under 40-45) has been associated with a 40-50% increased risk of CHD.[143,151] Women who experienced menopause between age 50-54 had decreased fatal CHD compared with those who experienced it at under 50-years-old.[143,145] A case control study found a linear inverse relationship between earlier menopause and increased CHD risk; each one year decrease in age at menopause and CHD was associated with a 2% increased risk of CHD.[152]

Surgical menopause is associated with a higher risk of CHD than natural menopause.[152] Women who have had a hysterectomy have a more than 10% increased risk of CVD; this risk more than doubles with hysterectomy and oophorectomy.[113,153]

Premature menarche

The average age of menarche is 13. Premature menarche (age younger than 10) is associated with increased CHD and CVD risk. Women who experience menarche before age 12 had increased all-cause mortality compared with menarche aged over 12.[154] Both early (age under 10) and late (age over 17) have been associated with increased relative risk of CHD.[155] Premature menarche is also associated with the development of hypertension, type 2 diabetes and hypercholesterolaemia, all of which increase CVD risk.[155]

Reproductive lifespan

A shorter reproductive lifespan mediated by early loss of oestrogen is associated with a higher CVD risk. A short reproductive lifespan (less than 30 years) is associated with an increased risk of non-fatal CVD events in mid-life, particularly in women with early menarche; and increased incident CVD compared with a reproductive lifespan of more than 42 years.[144,156] Women with a short reproductive lifespan (less than 33 years) and menarche at age under 11 had double the risk of incident CVD compared with a reproductive lifespan of 36-38 years and age of menarche at age over 13.[156]

AUTOIMMUNE DISEASE

Systemic autoimmune diseases are more prevalent in women particularly rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). This predisposes women to chronic inflammation, endothelial dysfunction, accelerated atherosclerosis and coronary microvascular dysfunction; clinically manifesting as premature CHD.[157-159] Diagnosis of an autoimmune disease is associated with an increased risk of CVD and all-cause mortality, with systemic connective tissue disorders and RA having the highest risk.[160] RA and SLE are associated with a significantly increased prevalence of traditional cardiovascular risk factors, plaque vulnerability, cardiovascular events and CAD.[161,162] The increase in cardiovascular events in these patients cannot be explained entirely by the increase in cardiovascular risk factors.[161]

Psoriasis is also an independent risk factor for MI, stroke, and CVD mortality, and is associated with an increased prevalence of cardiovascular risk factors.[163] In young, hospitalised patients with psoriasis, women were more likely to have multiple cardiovascular risk ▸

factors and ASCVD compared with men.[164] Chronic steroid therapy used in these conditions can worsen cardiovascular risk factors such as hyperglycaemia, hyperlipidaemia and hypertension, exacerbating the risk.[165]

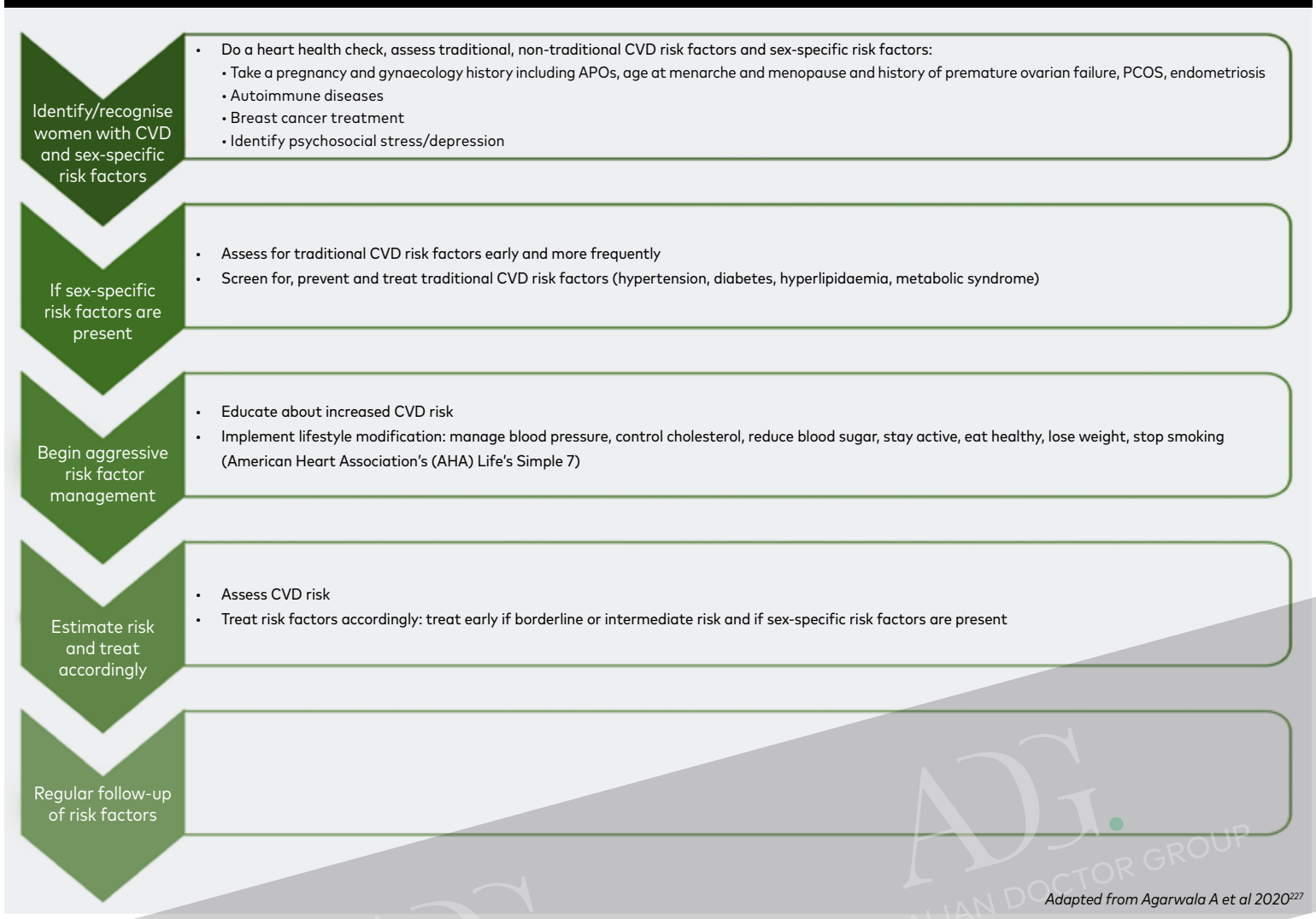
Rheumatoid arthritis

CVD is the leading cause of mortality in RA, accounting for 30-40% of deaths.[166,167] CVD mortality rates in patients with RA are 1.5-3-fold higher than matched controls, on par with the CVD risk imparted by diabetes.[168-170] Traditional cardiovascular risk factors are higher in RA, and additional cardiovascular risk (after adjusting for risk factors) is significantly increased in females.[171] The Nurses' Health Study found more than a twofold higher risk of MI in women with RA compared with non-RA, even after adjusting for cardiovascular risk factors.[172] Cardiovascular risk is closely linked to the severity and duration of flares of RA.[173] Chronic inflammation is hypothesised to exert direct and indirect effects on the vasculature and myocardium.[174] A lipid paradox has been described in patients with RA, where high levels of inflammation are associated with increased risk of CVD risk despite low to normal cholesterol levels.[175]

Systemic lupus erythematosus

Women aged 35-44 with SLE were 50 times more likely to have an MI, compared with their age-matched counterparts.[176] Women with SLE and hyperlipidaemia or hypertension have a significantly greater risk of cardiac events and CVD mortality.[177,178] The risk of MI and cardiovascular mortality is significantly higher in those with lupus nephritis.[179] There is an increased prevalence of detectable coronary artery calcium (CAC) in women with SLE.[180] Women with SLE and concomitant depression have an increased risk of developing subclinical atherosclerosis.[181]

Figure 2. Reducing cardiovascular risk in women



Adapted from Agarwala A et al 2020[227]

BREAST CANCER AND CVD

CVD and breast cancer have several overlapping risk factors (for example, obesity and smoking). Current breast cancer treatments have a negative impact on cardiovascular health,such as left ventricular dysfunction and accelerated CAD.[182] In older women, CVD poses a greater mortality threat than breast cancer; the risk of mortality from CVD is higher in breast cancer survivors than in women without a history of breast cancer; the greater risk manifests itself around seven years after diagnosis.[182]

Radiotherapy increases the risk of IHD. Coronary atherosclerosis and accelerated endothelial injury can occur as early as five years after exposure in breast cancer survivors who receive left sided thoracic radiotherapy; the risk persists for up to 30 years.[183] The risk is proportional to the mean dose to the heart, is greater in those irradiated on the left, and with pre-existing cardiovascular risk factors.[184] Radiotherapy has been associated with microvascular dysfunction (impaired coronary flow reserve, myocardial ischaemia and myocardial fibrosis); HFpEF; anthracycline-induced cardiotoxicity; acute and chronic pericarditis; valvular regurgitation and stenosis; conduction abnormalities and sudden death; especially with chest radiation doses greater than 30Gy.[183,185-187]

Chemotherapy agents (particularly anthracyclines and transtuzumab) have been associated with heart failure, hypertension and arrhythmias.[182] The risk of developing cardiac dysfunction is greater in those receiving high dose anthracyclines, high dose irradiation, sequential (low dose anthracycline and then transtuzumab)/combination therapy (anthracycline and radiotherapy), those aged over 60, those with more than two CVD risk factors, a history of MI, low normal ejection fraction and/or moderate valvular disease.[182]

Under-recognised risks

PSYCHOLOGICAL FACTORS

Depression, anxiety or panic disorder, hostility, anger, type A personality style, PTSD and psychological distress are associated with increased risk of CVD and incident IHD in both women and men.[188,189] Women generally have higher exposure to psychosocial stress and may be more vulnerable to its effects, and this tends to be a more important risk factor for CVD in women.[190]

Depression is more prevalent in women and has a greater contribution to CHD.[191,192] It is an independent risk factor for incident CHD in women.[193,194] A diagnosis of depression in a woman is associated with double the risk of CVD; the strength of the association between depression and CHD is of greater magnitude than any typical or atypical risk factor.[194,195] A study of midlife women with no history of CHD reported depression as the only significant predictive factor for CHD in women aged under 65.[196]

Psychosocial stressors, such as perceived stress and life events, have been associated with increased ASCVD risk.[197] Women, especially young women, are particularly vulnerable to the detrimental associations of mental stress and cardiovascular health.[198-200] Women appear to perceive greater psychological stress following an acute MI, which is associated with worse recovery and prognosis.[201] Women are more commonly affected by psychosocial disadvantages such as unemployment, chronic stress and insufficient social support, which contribute to greater depression and anxiety.[202,203]

PTSD has been associated with a 53% increased risk for incident cardiac events and cardiac mortality, which drops to 27% after adjustment for depression.[204] Trauma exposure and PTSD predict the onset of cardiovascular events in non-veteran women.[205] PTSD is associated with a 44% higher rate of developing incident IHD in women veterans.[206]

Living closer to roadways is associated with significantly increased risks of sudden cardiac death and fatal CAD in women.

Physical and psychological abuse, particularly intimate partner violence, is associated with increased incidence of CVD[207-209] Associated chronic stress and depression may directly affect the increase in CVD risk.[208] Intimate partner violence is associated with abdominal obesity, low HDL, high triglyceride (TG), higher blood pressure; these women are more likely to be smokers, engage in heavy or binge alcohol consumption, and are less likely to seek regular medical care.[210-212]

SOCIOECONOMIC AND CULTURAL STATUS, RACE AND POVERTY

Women are disproportionately affected by disparities in socioeconomic status and income.

Lower socioeconomic status and level of education in women is associated with an excess risk of CHD compared with men.[213] Women, especially those from a minority ethnicity, are over-represented among people living in poverty in high income countries. Low socioeconomic status, particularly low-level education and low income are associated with a higher incidence of and mortality from CVD.[214-215]

A large meta-analysis showed the association between low income, low levels of education and living in disadvantaged areas and CHD/CVD was stronger in women; there was a significantly greater excess risk for CHD associated with lower education in women than men.[216] Low socioeconomic status is strongly linked to cardiovascular risk factors and metabolic syndrome in women.[217,218] Women with lower and inadequate health literacy have an increased CVD risk and poorer health outcomes.[219-221]

ENVIRONMENTAL RISK FACTORS

Air pollution increases risk of CVD (CAD, heart failure, arrhythmias or cardiac arrest and stroke).[222,223] Long-term exposure to fine particulate air pollution is associated with an increased incidence of CVD and death in postmenopausal women without known CVD.[224] Living closer to roadways is associated with significantly increased risks of sudden cardiac death and fatal CAD in women (even after adjusting for risk factors).[225] Women are more likely to be affected by indoor air pollution from cooking.[226]

MANAGEMENT

Reducing cardiovascular risk in women

An approach to cardiovascular risk stratification appears in figure 2.

Traditional risk factors

Table 4 outlines the management of traditional risk factors.

Diet

Low consumption of salt and foods of animal origin and increased intake of plant-based foods – particularly whole grains, vegetables, fruit, legumes and nuts; and moderate consumption of fish, should be recommended and is associated with reduced atherosclerosis risk. Replacing butter and other animal fats with olive oil and vegetable oils rich in linoleic acid reduces CVD risk. Salt should be limited to less than 5g/day (equivalent to 2.3g sodium) and minimise the intake of red and processed meats, refined carbohydrates, and sweetened beverages to reduce ASCVD risk.[235]

MENOPAUSAL HORMONE THERAPY

Menopausal hormone therapy (MHT) is not recommended for CVD prevention; there is no demonstrated cardiovascular benefit and there may be potential harms such as increased CVD/stroke risk and breast cancer.[236-238] A 2017 meta-analysis showed that the increased risk of MHT outweighs any CVD prevention benefit.[239] The increased risk of venous thromboembolism with MHT has been shown for all types of MHT, except transdermal oestrogen.[240]

ASPIRIN

Prescribe aspirin (secondary prevention) for women with established ASCVD as it reduces subsequent vascular events.[241] Consider it in those with high ASCVD risk, current smokers, strong family history of premature ASCVD, high CAC score (more than 100) or carotid plaque, suboptimal control of lipids or blood pressure and low risk for bleeding.[64]

Aspirin is not recommended for primary prevention of ASCVD in healthy women with no major CVD risk factors, routinely after 70, or in those with prior bleeding/risk of bleeding.

Adverse pregnancy outcomes

The management is outlined in figure 3.

Table 4. Management of traditional risk factors

Traditional risk factor	Management
Hypertension	Maintain normal BMI, weight loss to achieve ideal body weight (BP drops 1mmHg per 1kg weight loss) Moderate salt intake (less than 1500mg/day) or reduce by 1000mg/day Regular physical activity (90-150min/week — including aerobic and resistance exercise) No more than one alcoholic drink a day DASH (dietary approaches to stop hypertension) diet — rich in fruits, vegetables, whole grains, and low-fat dairy products, with reduced saturated and total fat[228] Screen with ambulatory blood pressure monitoring Pharmacotherapy in those with high cardiovascular risk and stage 2 hypertension (BP more than 140/90mmHg); concomitant diabetes, chronic kidney disease, IHD, or heart failure Therapeutic target: less than 130/80mmHg[229] Reduce exposure to air pollution Oral contraceptive pill (OCP) is associated with an increase in blood pressure, so monitor blood pressure in all patients on an OCP[230]
Diabetes	Aggressive management of CVD risk factors: • HbA1c less than 7.0%[231] • Hypertension: treat if BP is above 130/80mmHg[231] — Goal BP is less than 130/80mmHg[232] — In those aged over 65 the goal is 130-139mmHg systolic[233] • Lipids and LDL: — Age over 40 (no ASCVD risk factors): moderate intensity statin — Age over 40 (ASCVD risk factors): high intensity statin — Age under 40: no ASCVD risk factors, no statin; if risk factors are present, prescribe a statin[234] — Target LDL: very high risk less than 1.4mmol/L; high risk less than 1.8mmol/L, moderate risk less than 2.5 mmol/L[233] — Aspirin in very high/high risk[233] American Diabetes Association (ADA) definition of ASCVD risk factors: LDL more than 100mg/dL, high blood pressure, smoking, chronic kidney disease, albuminuria and family history of premature ASCVD[235] European Society of Cardiology (ESC) definitions: Very high risk: target organ damage or three or more risk factors or type 1 diabetes duration of more than 20 years. High risk: diabetes duration of more than 10 years without target organ damage and any other risk factor. Moderate risk: type 1 diabetes and under 35 years of age, type 2 diabetes and under 50 years of age with diabetes duration of less than 10 years duration without other risk factors
Hyperlipidaemia	Lifestyle modification: diet, exercise and weight loss Statin therapy is recommended (ACC/AHA guidelines),[234] in addition to lifestyle modification, in the following groups: • Clinical ASCVD • Severe hypercholesterolaemia (LDL more than 4.9mmol/L) • Diabetes mellitus in adults (aged 40-75) • Primary prevention in adults aged 40-75 at high risk (more than 20%), some adults at intermediate risk (7.5-20%) or borderline risk (5%-less than 7.5%) based on the presence of risk enhancers*, the presence of an elevated CAC and if clinician patient risk discussion favours a statin[230,236,238]
Obesity	Calculate BMI annually (or more frequently in the overweight/obese); consider measuring waist circumference to identify those at higher cardiometabolic risk Counselling and comprehensive lifestyle interventions, including caloric restriction, physical activity, to achieve and maintain weight loss[230] Consider bariatric surgery
Physical activity	Adults to engage in at least 150 minutes per week of moderate-intensity (eg, brisk walking, biking, dancing or swimming) or 75 minutes per week of vigorous-intensity aerobic physical activity (jogging/running, biking more than 16km/hour, swimming laps); or an equivalent combination of moderate and vigorous activity to reduce ASCVD risk[230] Decrease sedentary behaviour (this is defined as any waking behaviour characterised by an energy expenditure equal to or less than 1.5 metabolic equivalents (METs) while sitting, reclining or lying)[230]
Smoking	Firmly advise smoking cessation and avoidance of second-hand smoke Advise counselling, nicotine replacement and other pharmacotherapy +/- behavioural therapy at each healthcare encounter[230]

**Risk enhancers: (2019 ACC/AHA primary prevention guidelines)[230]*
- Family history of premature ASCVD (under 55 in male first degree relative, under 65 in female first degree relative)
- Primary hypercholesterolaemia or persistently elevated LDL-C (more than 4.1mmol/L)
- Chronic kidney disease (stage III or IV)
- Metabolic syndrome (three or more of increased waist circumference, non-fasting TG more than 1.7 +/- low HDL 1.3mmol/L in women, elevated blood pressure or BSL)
- Women specific risk factors that increase ASCVD risk (eg, premature menopause, pregnancy associated conditions)
- Inflammatory diseases (especially RA, psoriasis, SLE)
- High risk race/ethnicity (South Asian ancestry)
- Biomarkers (persistently elevated TG above 2.0 non-fasting, elevated high-sensitivity C-reactive protein (hsCRP), elevated lipoprotein(a), elevated apolipoprotein B, ankle-brachial index less than 0.9)

Autoimmune disease

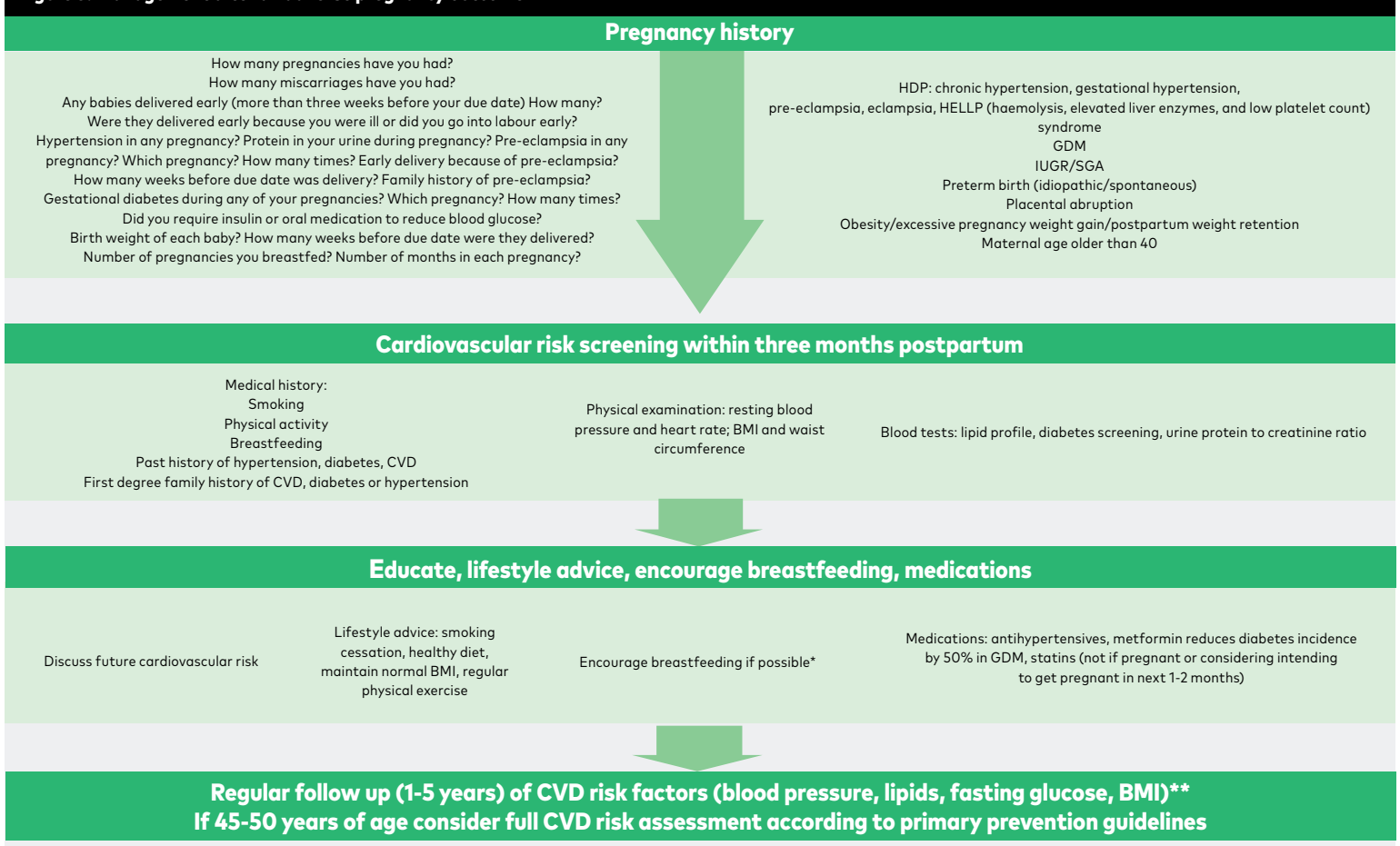
Primary prevention guidelines consider autoimmune diseases as risk enhancers, so the presence of systemic inflammatory and autoimmune disorders should be considered in CVD risk assessment.[230] Screen women with autoimmune disorders and aggressively manage other cardiovascular risk factors as well as controlling disease activity and inflammation (see figure 4).[252] CVD risk assessment is recommended for all patients with RA and psoriatic arthritis (at least once every five years). Encourage lifestyle modifications.

Treating RA with disease-modifying antirheumatic drugs (DMARDs) may lower the risk of CVD by decreasing chronic inflammation. These include methotrexate, biologic DMARDs such as tumour necrosis factor (TNF) alpha, IL-1 (interleukin) and IL-6 and targeted synthetic DMARDs.[253] Aggressive RA control with DMARD therapy is recommended but NSAIDs and glucocorticoids should be used with caution.[254]

Polycystic ovarian syndrome

Metformin may offer the greatest benefit in high metabolic risk groups including those with diabetes risk factors, IGT, or high-risk ethnic ▸

Figure 3. Management after an adverse pregnancy outcome



**Encourage breastfeeding if possible; lifetime breastfeeding for more than 12 months decreases CVD, hypertension, hyperlipidaemia and diabetes.[243] Breastfeeding has been associated with a dose dependent decrease in diabetes and progression of type 2 diabetes; a reduction in CVD risk; lower maternal risk of CVD hospitalisation and mortality in middle-aged and older women; and decreased indicators of cardiovascular risk.[244-248]*
***Consider annually or every few years especially in the presence of HDP or GDM.[249]*

Adapted from Cho L et al 2020[64], American College of Obstetricians and Gynecologists 2019[241], American College of Obstetricians and Gynecologists 2018[242]

groups.[255] Screen patients with PCOS for CVD risk including monitoring for weight changes every 6-12 months, annual measurement of blood pressure, blood glucose and lipids and assessment of smoking and physical activity. Encourage lifestyle changes. Also consider psychological factors (anxiety, depression and eating disorders), which are prevalent.[255] Consider obesity medications following lifestyle changes.

Breast cancer patients/ survivors

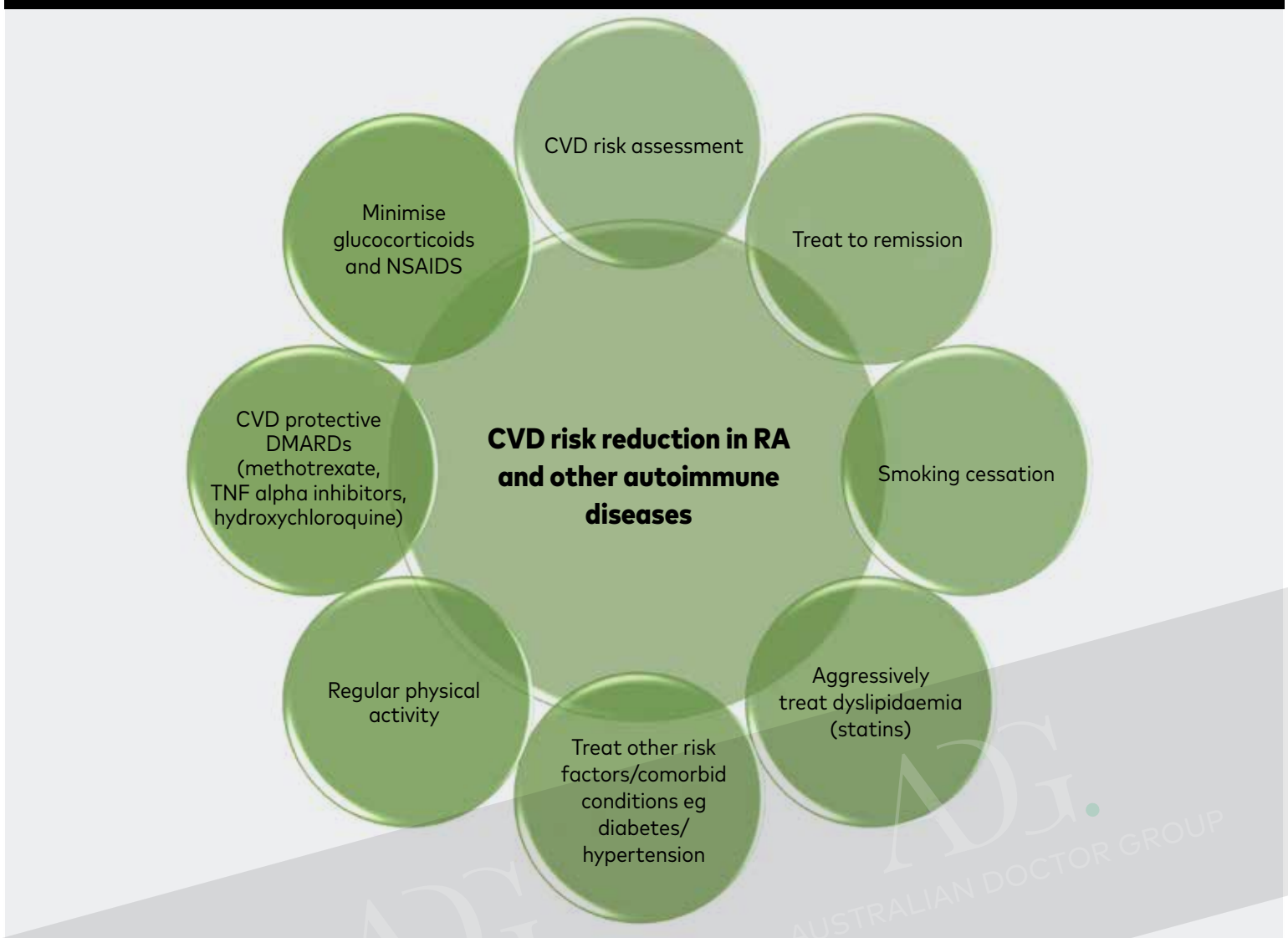
Management requires a multidisciplinary specialist approach. Stress test high risk patients 5-10 years post-chest radiotherapy. Perform echo surveillance (with strain imaging) before, during and after anthracycline and human epidermal growth factor receptor 2 (HER-2) directed therapy, with cardiology consultation if ejection fraction is less than 53%. Perform annual cardiovascular assessments after patients have completed therapy.[182]

Depression and psychological issues

Recognise depression and psychosocial stressors in women. Depression is a risk factor and has prognostic implications for CVD, so screen for and treat depression as indicated.[256]

Promoting a healthy lifestyle and managing mental health issues will improve a patient's quality of life, may improve health outcomes and prevent CVD.

Figure 4. CVD risk reduction in auto-immune disease



CASE STUDY

JANE, 55 presents for a repeat antidepressant prescription. She has been asymptomatic, but her notes record a history of pre-eclampsia during pregnancy with both her children. She went through menopause at 51.

Her BP is 160/90mmHg, heart rate 60 and regular and BMI 25kg/m². Her total cholesterol is 6.5mmol/L (optimum is less than 4.0) and LDL is 4.5mmol/L (population reference 2.0-3.4, therapeutic targets less than 2.5 depending on risk). Fasting blood sugar is 6.5mmol/L (normal 3.0-5.4) and HbA1c 6.0% (normal 3.5-6.0%) and urine albumin creatinine ratio 5mg/mmol (normal less than 3.5).

Jane's 24-hour blood pressure monitor confirms mild hypertension. She is advised to increase her exercise and make dietary changes to help reduce her blood pressure, cholesterol and sugar levels.

Given her risk factors, a coronary calcium score is performed. This is 700, indicating severe atheroma, and puts her in the 99th percentile for her age and gender. An echocardiogram shows normal systolic function, mild hypertensive changes and no significant valvular abnormalities A stress echocardiogram shows no reversible ischaemia.

On review two months later, Jane's BP is 150/85mmHg and her LDL 4.2mmol/L, and HbA1c is down to 5.2%. An oral glucose tolerance test is normal.

Jane is started on an ACEI, a statin and aspirin. She will require regular follow-up and continued aggressive management of her risk factors as she is at high risk.

CONCLUSION

CVD is the second most common cause of death in Australian women. There is abundant literature reporting gender disparities in outcomes, quality of care and traditional cardiovascular risk factors. There are both women specific and non-traditional risk factors for ASCVD that disproportionately affect women.

Early identification of these risk factors and their aggressive modification with lifestyle, medication and regular follow up will help lower the lifetime risk of CVD and reduce the burden of CVD in women.

RESOURCES

- **How to Treat article by Dr F Foo, Environmental change and cardiovascular disease** bit.ly/3m1V7rE

References

Available on request from howtotreat@adg.com.au

How to Treat Quiz.

CARDIOVASCULAR RISK IN WOMEN

GO ONLINE TO COMPLETE THE QUIZ **ausdoc.com.au/howtotreat**

1. **Which THREE statements regarding CVD in women are correct?**
   - **a** IHD is the leading cause of death in Australian women.
   - **b** Women are more likely to die within one year of their first MI.
   - **c** Around 20% of CHD events in women occur in the absence of conventional risk factors.
   - **d** Current tools are inadequate at assessing risk in young women.

2. **Which THREE ASCVD risk factors are specific to women?**
   - **a** APOs.
   - **b** Autoimmune disorders.
   - **c** Short reproductive lifespan.
   - **d** Endometriosis.

3. **Which THREE are gender disparities regarding traditional risk factors for ASCVD are correct?**
   - **a** Women with diabetes are more likely to develop and die from CVD.
   - **b** Women are less likely to achieve lipid targets.
   - **c** Tobacco use is a more potent risk factor for women.
   - **d** Hypertension is a more potent risk factor for MI in men.

4. **Which ONE is not an associated future risk of all HDP?**
   - **a** Future hypertension.
   - **b** Myocarditis.
   - **c** Diabetes.
   - **d** Hyperlipidaemia.

5. **Which TWO statements regarding women specific risk factors are correct?**
   - **a** Seventy per cent of women with GDM 1 develop type 2 diabetes 10 years postpartum.
   - **b** The greatest relative risk reduction in CVD mortality conferred by parity occurs with the fifth and subsequent pregnancies.
   - **c** Pre-pregnancy overweight or obesity and diabetes increase the risk of GH.
   - **d** A history of miscarriage or stillbirth increases the risk of CHD and stroke.

6. **Which THREE statements regarding non-pregnancy related CVD risk factors are correct?**
   - **a** CVD risk increases after menopause.
   - **b** Autoimmune disease is associated with an increased risk of CVD and all-cause mortality.
   - **c** Diabetes does not occur in lean women with PCOS.
   - **d** In older women, CVD poses a greater mortality threat than breast cancer.

7. **Which TWO are under-recognised risks for CVD?**
   - **a** Chemotherapy agents.
   - **b** Psychological stress.
   - **c** Radiation treatment.
   - **d** Socioeconomic and cultural status, race and poverty.

8. **Which THREE are targets for management in CVD risk reduction?**
   - **a** BP less than 130/80mmHg.
   - **b** HbA1c less than 7.0%.
   - **c** At least 150 minutes per week of vigorous-intensity aerobic activity.
   - **d** Smoking cessation and avoidance of second-hand smoke.

9. **Which TWO medications are indicated in the management in CVD risk reduction?**
   - **a** Aspirin for secondary prevention in established ASCVD.
   - **b** Menopausal hormone therapy.
   - **c** Aspirin for primary prevention in the absence of major CVD risk factors.
   - **d** Statin.

10. **Which THREE strategies may be beneficial in managing CVD risk in women?**
    - **a** Screen for and treat depression.
    - **b** DMARDs where indicated in autoimmune disease.
    - **c** Discourage breastfeeding.
    - **d** Metformin for PCOS in high metabolic risk groups.

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