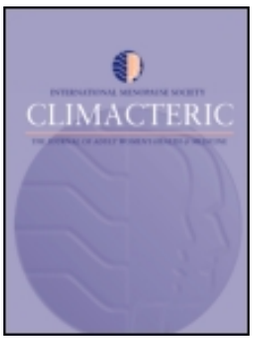

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REVIEW

Cardiovascular risk assessment in women – an update

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ABSTRACT

Cardiovascular disease is the leading cause of morbidity and mortality in postmenopausal women. Although it is a disease of aging, vascular disease initiates much earlier in life. Thus, there is a need to be aware of the potential to prevent the development of the disease from an early age and continue this surveillance throughout life. The menopausal period and early menopause present an ideal opportunity to assess cardiovascular risk and plan accordingly. Generally in this period, women will be seen by primary health-care professionals and non-cardiovascular specialists. This review addresses female-specific risk factors that may contribute to the potential development of cardiovascular disease. It is important for all health-care professionals dealing with women in midlife and beyond to be cognisant of these risk factors and to initiate female-specific preventative measures or to refer to a cardiovascular specialist.

KEYWORDS

Cardiovascular disease; female-specific cardiovascular risk factors; management; smoking; hypertension; lipids; diabetes mellitus; age at menarche; polycystic ovary syndrome; menopausal symptoms; menopausal hormone therapy; coronary heart disease; stroke

Introduction

Cardiovascular disease (CVD) is a leading cause of mortality in postmenopausal women[1]. Typically women are 9–10 years older than men at first presentation of atherosclerotic coronary heart disease[2], and this is related to the number of years passed since the last menstrual period and, at least in part, related to the decline in ovarian hormone concentrations during the menopausal transition and beyond[3,4]. As CVD risk factors are affected by hormonal status and other common, female-specific co-morbidities, a more gender-specific approach is justified for optimal prevention and treatment of CVD in women. This article will briefly review our current knowledge of the importance of conventional CVD risk factors, with a focus on women, and will highlight stages in a woman's life where clues to the development of CVD risk factors become evident. In an effort to improve prevention and management of CVD in women, we must encourage all physicians to engage in more intensive CVD risk assessment and management of women, at all times but particularly at midlife.

Conventional risk factors for cardiovascular disease

Women should be aware of risk factors for CVD and the appropriate actions to reduce risk, with the emphasis on self-monitoring. A heart-friendly lifestyle should be promoted in women of all ages. As well as advice from health professionals, websites from national and international societies, such as the World Heart Federation, use knowing your 'Heart Age' as a means of motivation to individuals to take responsibility for their own future health (http://www.world-heart-federation.org/cardiovascular-health/heart-age-calculator/).

Smoking

Smoking remains one of the most preventable and powerful risk factors for atherosclerotic cardiovascular diseases. Globally, more men than women are smokers in most countries, although there is more equivalence between genders in Europe and the Americas (http://www.who.int/topics/tobacco/en/). The World Health Organization (WHO) reports that young boys and girls (aged 13–15 years) smoke at the same rates in more than half of the countries of the world, warning that trends in health behavior are always vulnerable to social change (http://www.who.int/topics/tobacco/en/). The complex interplay between cigarette smoking and atherosclerosis is not entirely clear; however, smoking is known to induce vascular dysfunction[5,6] and affect proatherogenic factors[7].

Hypertension

Among the traditional risk factors for CVD, hypertension is as powerful in women as in men and is generally under-diagnosed and under-treated[8,9]. In developed countries, 30% of adult women have hypertension and this prevalence is even higher in low-middle-income countries, reaching up to

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53%[10,11]. For every 20 mmHg systolic and 10 mmHg diastolic blood pressure increase, there is a doubling of mortality both from coronary heart disease (CHD) and stroke for women and men aged 40–89 years[12]. Although younger women are at lower absolute cardiovascular risk than older women[1], this should not impede the detection and effective management of hypertension at any age. In particular, physicians should be vigilant for arterial hypertension in women with a history of hypertensive pregnancy disorders (discussed later)[13]. The prevalence of hypertension in postmenopausal women is more than twice the prevalence in premenopausal women[14]. Monitoring and control of blood pressure are imperative in women at all ages and effective blood pressure control in the premenopausal period, in the menopausal transition or the early postmenopause will prevent CVD developing at an older age. Even moderate or borderline hypertension (<140/90 mmHg) causes more endothelial dysfunction and cardiovascular complications in women than in men[15].

Management

The benefit of treating hypertension in women has been shown to be at least equivalent to that in men[16] or even more beneficial than in similarly aged men[8]. Currently, the rate of adequate blood pressure control among treated hypertensive women is inadequate, not only in low- and middle-income countries but also in developed countries[10,11]. The rate of hypertensive women detected, treated and subsequently well controlled is estimated to be only 10%[11]. This represents an enormous missed opportunity in cardiovascular disease prevention. The European Society for Hypertension (ESH) and the European Society of Cardiology (ESC) address the specific case of women in their recent guidelines for the management of arterial hypertension, summarizing the evidence and detailing recommendations on treatment strategies in hypertensive women[13]. Briefly, commonly used drug regimens for treating hypertension, based on angiotensin-converting-enzyme (ACE) inhibitors, calcium antagonists, angiotensin receptor blockers, diuretics and beta-blockers are just as effective in women as in men, although ACE inhibitors and angiotensin receptor blockers should be avoided in women of child-bearing potential[13,16]. The specifics of managing hypertension in pregnancy are discussed elsewhere[13].

Lipids

The incidence of raised total cholesterol concentration ≥6.5 mmol/l is equivalent or greater in women compared to men aged 50 years and older in the UK and USA (WHO Global Infobase; https://apps.who.int/infobase/Indicators.aspx). The evidence for a relationship between lipid profile and CHD risk is derived largely from studies of men, but there are differences in the particular lipid profiles that are associated with increased CHD risk in men and women. The association between the concentrations of total cholesterol and low density lipoprotein (LDL) cholesterol and CHD death is less strong in women than in men; plasma concentrations of high density lipoprotein (HDL) cholesterol are generally a better predictor of cardiovascular mortality in women[17–19]. Concurrently, elevated triglycerides may be an independent risk factor for CHD mortality in women, particularly in women with low HDL cholesterol concentrations[20].

Management

Historically there has been a paucity of data evaluating the impact of lipid lowering on primary and secondary prevention of CHD in women; however, a recent meta-analysis suggests that the overall benefit derived from lipid-lowering therapy is similar in women and men, mainly relating to CHD prevention and not CVD in general[21]. The JUPITER trial, a study of statin use in a healthy population with elevated high-sensitivity C-reactive protein, included a large female subgroup and reported a 12% reduction in relative risk of total mortality in high-risk subjects with statin use, with no difference in the treatment effect between women and men[22]. Current European guidelines on the management of dyslipidemias considered a number of meta-analyses, including one that incorporated JUPITER, and recommend considering statin use for primary prevention in women at high CVD risk[21–23], and routinely prescribing a statin-based lipid-lowering regimen to women for secondary prevention of cardiovascular events, with the same recommendations and therapeutic targets as for men[23]. While other non-statin lipid-lowering drugs may be used, at present the evidence for a cardioprotective effect of lipid lowering in women is limited to statins[23]. Some postmenopausal hormone therapy (MHT) formulations beneficially affect lipid profiles, with decreases in LDL cholesterol which are modest compared with statins[24]. However, MHT produces significant increases in HDL cholesterol and decreases in lipoprotein(a) whilst statins have little effect. MHT can therefore be considered for lipid lowering in postmenopausal women with mild to moderate hypercholesterolemia, although the beneficial effects of MHT on the cardiovascular system are due to a number of factors including, but not confined to, lipid lowering. Due to lack of data on possible side-effects, lipid-lowering medications are not advised in pregnancy and during breast-feeding[23].

Diabetes mellitus

Diabetes mellitus (DM) is linked with increased morbidity and mortality from CVD in both men and women[25,26]; however, women with diabetes appear to be at a greater relative risk of CVD than men[27]. Most studies show a higher CVD risk in postmenopausal women than premenopausal women with DM[28–30]; however, it is unclear whether this disparity is due to estrogen deficiency or age[31]. Hormone therapy did not decrease CVD risk in a study of women with established DM, suggesting that ovarian hormones may not be involved[32]. Other purported explanations for sex differences in CVD risk in diabetics have been well reviewed previously[27] and include a less favorable lipid profile in women[27], differences in inflammatory marker concentrations[33,34], lower adherence to diabetic treatment in women[35,36], and women being more likely to have multiple risk factors for CVD[37]. Interestingly, postprandial glucose appears to be a stronger predictor of CVD in diabetic women than men, whereas HbA1c is a better

predictor of stroke in diabetic women compared with diabetic men[38–40].

Management

Current guidelines on management of diabetes do not distinguish between the sexes, evidently because studies have not conducted gender-specific analyses[41]. Metformin remains the first-choice drug for glucose lowering in those with unimpaired renal function, particularly the overweight type 2 diabetes sufferers; however, a combination of glucose-lowering medication is often required to reach glucose targets[41]. We do not know whether insulin-sensitizing agents such as metformin are effective as a sole therapy in reducing the risk of CVD in women, as the studies have not been performed. The current controversies and complexities surrounding diabetes management, including prevention of CVD in patients with diabetes, are described comprehensively elsewhere[41].

Reproductive years

Age at menarche and CVD risk

World-wide, a decline in age of first menstruation is observed that is primarily attributed to deterioration in life-style factors and environmental toxic agents[42,43]. Conflicting data exist on the long-term impact of age at menarche and consequent CVD risk[44–46]. A recent meta-analysis demonstrated an inverse relationship between age at menarche and risk of all-cause death, showing a 23% higher relative risk (RR) of death in women with early menarche (<12 years) but no protection of late menarche[46]. Although there was an inverse association between age at menarche and ischemic heart disease (IHD) death in non-smoking women or women with low prevalence of smoking (24% higher RR of death from IHD in the earliest menarcheal age group), there was no convincing association between cardiovascular mortality and menarcheal age[46]. In a recent large, prospective UK study, both early (≤10 years) and late (≥17 years) menarche were associated with increased risk of vascular disease, with a weaker association for cerebrovascular and hypertensive disease than for CHD[47]. Genetic factors, obesity and smoking may at least partially explain any association between age of menarche and CVD risk[48,49].

Other issues

Issues that occur during the reproductive years which may affect cardiovascular risk in midlife include a history of polycystic ovary syndrome (PCOS), which is commonly associated with insulin resistance, leading to increased risk of glucose intolerance, diabetes and lipid abnormalities which, in turn, may lead to atheromatous CHD[50]. Metformin can be beneficial in women with PCOS and impaired glucose tolerance[51]. Whether the clustering of CHD risk factors in PCOS translates into an increase in cardiovascular events is still unclear, however.

In women who develop hypertensive pregnancy disorders or gestational diabetes, vascular endothelial dysfunction occurs in both the uterine and maternal circulations, potentially leading to impaired vascular health and initiation of the atherosclerotic process[52–55]. Epidemiological studies show a positive association between pre-eclampsia and increased risk of CVD (comprehensively reviewed recently[56]). Gestational diabetes mellitus confers a four- to seven-fold higher risk of future type II diabetes and the development of the metabolic syndrome in midlife[57,58]. Pregnancy-related disorders offer a unique opportunity for increasing the awareness of increased cardiovascular risk and promoting early preventive cardiovascular measures, and consequently have been incorporated in the 2011 American Heart Association (AHA) guidelines for the prevention of CVD in women, and the 2014 AHA guidelines for stroke prevention[9,59].

Menopause and postmenopausal years

Age at menopause and CVD risk

The average age of the menopause is approximately 51 years. Premature menopause (aged <40 years), either natural or surgical, has been associated with elevated CVD risk[3,60–62]. In women with premature surgical menopause, estrogen therapy was associated with significant protection against ischemic heart disease[62]. The benefit from estrogen was most pronounced for current users and for women who started treatment within 1 year after surgery[62]. Approximately 1% of 40-year-old women have spontaneous primary ovarian insufficiency (POI; ovarian failure before age 40 years)[63], and these women have impaired endothelial function and early onset of CHD[3,64]. Although long-term follow-up data are relatively scarce, a recent meta-analysis showed that POI is associated with a modest increased risk for CHD (hazard ratio (HR) 1.61, 95% confidence interval (CI) 1.22–2.12), but not for stroke[65]. In addition to POI, women who have had a prophylactic bilateral oophorectomy before the age of 40 also have an increased risk for CVD[62,66].

Menopausal symptoms and CVD risk

Classic vasomotor symptoms of the menopausal transition such as hot flushes and night sweats are experienced by approximately 40% of perimenopausal and menopausal women world-wide[67]. Current literature suggests a link between menopausal vasomotor symptoms and adverse CVD risk profile, although not all studies are concordant. In a cohort study of 5523 women aged 46–57 years, severe menopausal symptoms were associated with hypertension, elevated total cholesterol levels and increased CVD events compared to women with few or no menopausal symptoms[68]. Follow-up of over 10 000 healthy women of menopausal age over 10 years showed that night sweats but not hot flushes were associated with a modest increase in CHD risk[69]. Hot flushes have been associated with a higher estimate of insulin resistance and serum glucose, independent of body mass, serum estradiol and follicle stimulating hormone over a period of 8 years[70]. Signs of subclinical atherosclerosis are more prevalent in women with severe vasomotor symptoms in some but not all studies[7,71–75].

Menopausal vasomotor symptoms are associated with increased sympathetic and decreased parasympathetic function that may increase the risk of cardiovascular events[70,76], a fact that may be particularly important during a hot flush episode in women prone to severe arrhythmias[76,77].

Update on menopausal hormone therapy and cardiovascular disease risk

Coronary heart disease

The use of MHT for prevention of CHD remains controversial. Observational studies of menopausal women taking clinically indicated MHT consistently show reductions in the occurrence of cardiovascular disease events[78,79] and CHD death[80] and some show similar reductions in all-cause mortality[81,82]. The argument for a favorable effect of MHT was strengthened by scientific data showing favorable effects of estrogens on CVD risk factors such as lipid profile and vascular function[83]. Epidemiological and observational studies can be subject to bias, however, and so randomized studies were called for. Subsequent secondary prevention studies such as the Heart Estrogen/progestin Replacement Study (HERS) and Estrogen Replacement in Atherosclerosis (ERA), conducted in women with established CHD in their sixties, showed a null effect of combination conjugated equine estrogens (CEE) plus medroxyprogesterone acetate (MPA) or CEE alone on atherosclerosis progression[84,85]. The largest randomized trial to report was the Women's Health Initiative (WHI) hormone trial, a placebo-controlled study examining the effects of MHT (CEE + MPA, or CEE alone) on primary CVD prevention, osteoporotic fractures and breast cancer risk. The WHI was stopped early due to an excess of invasive breast cancer in women taking CEE + MPA, leading to women around the world stopping MHT, or not starting it, and confusion within the medical community about what to advise patients[32,86,87]. With time and the accumulation of further evidence, however, patterns have emerged that may guide physicians on how to treat their patients today.

One key factor determining the effects of MHT on CVD risk is the timing of initiation of MHT, the so-called 'timing hypothesis'. In the WHI, the mean time since menopause of participants was 13 years; re-analyses of the WHI found a non-significant reduction in CHD risk in the group of women initiating combined MHT within 10 years from menopause[88], whilst a follow-up of those women who initiated estrogen-alone MHT below age 60 years showed a significant reduction in CHD compared with those randomized to placebo[89]. Additionally, a meta-analysis of 23 studies demonstrated a reduction in CHD events in postmenopausal women initiating hormone therapy below age 60 years[90]. Interestingly, in women initiating therapy above age 60 years, hormone therapy increased CHD events in the first year of treatment, followed by a decreased risk after 2 years and beyond[90]. A more recent Cochrane review confirmed a reduction in CHD with hormone therapy initiated within 10 years of the onset of menopause[91]. The prospective Kronos Early Estrogen Prevention Study (KEEPS) reported that MHT initiated in recently menopausal women with low CVD risk reduced menopausal symptoms and some markers of CVD risk, but had no effect on atherosclerosis progression compared with placebo after 4 years of treatment[92]. In the Danish Osteoporosis Prevention Study (DOPS), women who were 7 months postmenopausal were randomized to estradiol, with or without norethisterone acetate, or no treatment[93]. At 10-year follow-up, there was a significant reduction in the composite endpoint of mortality, myocardial infarction, and hospitalization for heart failure with no increased risk of cancer (including breast cancer) or death[93]. At 16 years' follow-up, these benefits remained with no increased risk of breast cancer or stroke[93]. The Early versus Late Intervention Trial with Estradiol (ELITE) study, a clinical trial designed to test the hormone-timing hypothesis, recently reported a reduced rate of carotid intimal medial thickness progression in women given MHT within 6 years of menopause compared with placebo, and compared to women who were $\geq$10 years since menopause[94]. Together, the accumulating evidence suggests that initiation of MHT early after menopause may beneficially affect CVD risk.

The 'timing hypothesis' appears important when considering MHT effects on mortality. It is noteworthy that even in the WHI – which included women with a mean age of 63 years – the mortality in the intervention group was not increased (HR 0.98, 95% CI 0.70–1.37)[86]. In a meta-analysis of 19 randomized trials of postmenopausal women, mortality was significantly reduced in the women on MHT aged under but not over 60 years[95]. This is supported by a recent observational study with over 290 000 MHT users showing that protection against cardiovascular mortality was more pronounced in younger MHT users[96]. Furthermore, a recent Cochrane review also showed a significant reduction in all-cause mortality in women initiating MHT within 10 years of the onset of menopause[91]. It has been estimated that 'the avoidance of estrogen' in newly postmenopausal women (age 50–59 years) following the publication of the WHI in 2002 has led to almost 60 000 excess deaths in women in the US during a 10-year period[97]. Further, evidence from a Finnish population-based, observational study suggests a transient increase in risk of CVD mortality in women who discontinue postmenopausal HT[98].

Stroke

Currently, there is little robust evidence to support the use of MHT in the prevention of stroke, with much of the information coming from studies of CHD with stroke as a secondary or safety endpoint. A recent observational study of women taking clinically indicated MHT showed a reduced risk of death due to stroke[80]. Studies in women with established vascular disease such as the HERS and the Women's Estrogen for Stroke Trial (WEST) showed similar stroke events in women taking MHT versus placebo[85,99]. In women without a history of CVD enrolled in the WHI, ischemic but not hemorrhagic stroke was increased in women taking MHT when the study stopped, but after further follow-up there was a null effect of MHT on stroke risk[89]. Stroke was a secondary

endpoint in DOPS and no increase was shown in stroke risk with estradiol with or without norethisterone acetate[93]. There is evidence that the route of administration of MHT may be important – risk of ischemic but not hemorrhagic stroke may be increased by oral MHT but not by transdermal estradiol[100] – but no studies have investigated this specifically. The 2014 AHA guidelines for the prevention of stroke in women do not recommend MHT for stroke prevention based on the summation of current evidence, although they acknowledge that MHT should not be denied to women who require it for other reasons, dependent on an evaluation of the risks and benefits[59].

Summary

In summary, the potential benefits of MHT on CVD risk and mortality must be weighed against the risks. This review does not address the known risks of some forms of MHT nor the other known benefits of this therapy. Treatment advice should be provided on an individual basis, depending on the presence of symptoms and evaluation of potential adverse cardiovascular risk[101–103].

Conclusions

Cardiovascular disease is the leading killer of women in the western world. Prevention must be addressed in women as for men from a young age, by discouraging smoking and promoting a heart-friendly lifestyle that includes a healthy diet and regular physical activity. Health professionals, and women themselves, should be aware of women-specific factors that can affect CVD risk, and ensure that risk factors are assessed at all contacts with health-care providers. Management of CVD risk factors is similar in women and men, and it is as important for women to manage their risk factors as it is for men.

Recommendations

- A heart-friendly lifestyle should be promoted in women of all ages. Women should know their 'Heart Age' (http://www.world-heart-federation.org/cardiovascular-health/heart-age-calculator/);
- Women should be aware that CVD is the leading killer of women;
- Women should be aware of risk factors for CVD and the appropriate actions to reduce risk, with the emphasis on self-monitoring;
- Women should be assessed for CVD risk factors at all contacts with health-care providers but particularly in midlife and beyond;
- Health-care providers should have knowledge about gender-specific differences concerning the presentation and management of CVD.

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