CPD Article

Reducing the risk of cardiovascular disease in older women

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Abstract

Cardiovascular disease (CVD) is the leading cause of death in women older than 50 years. Risk factors for CVD differ in some aspects from those in men. The prevention of CVD in women has undergone a reappraisal with the publication of studies looking at the use of menopausal hormone therapy for both primary and secondary prevention. Although these studies concluded that there was no place for the use of hormone therapy for prevention of CVD, recent data suggests that the issue is still not resolved as regards the younger woman in early menopause. Until more data is available in this regard, the main focus of prevention should be on interventions to decrease risk factors for cardiovascular disease.

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Introduction

Cardiovascular disease (CVD) includes hypertension, coronary heart disease (CHD), atherosclerosis and stroke. It is the leading cause of death in women who are more than 50 years of age in Western countries.[1] CVD accounts for 53% of female deaths. Using the figures supplied by the American Heart Association, in the year 2003, 484,000 women died of CVD the USA.[2] This is approximately 57,000 more than the number of men who died of the same condition. Whereas death rates in men from CVD have shown a progressive decrease since 1980, death rates in women from this condition have remained constant. In spite of this, both patients and health care providers continue to underestimate the extent of this problem in women, where the focus is more on breast cancer, and health care providers still considering this predominantly a disease in men.

Prior to menopause, the incidence of CVD in women is lower than seen in men.[2] Incidence becomes similar in men and women between 45 and 55 years of age. Thereafter more women have CVD than do men.

Risk factors of CVD in women

1. Menopause

The onset of menopause at any age earlier than 55 years results in an increase in the incidence of CVD. As an example, in the Framingham study, in a sample of 2873 women, in all age groups the incidence of CHD was lower in premenopausal than in postmenopausal women.[3] This was especially marked in the 40 - 44 year group but even in the 45 - 49 and 50 - 54 year groups the incidence in postmenopausal women was double that seen in premenopausal women.

2. Dyslipidaemia

The onset of menopause results in an unfavourable shift in lipid levels. Total cholesterol, low density lipoprotein cholesterol (LDL), and triglycerides (TG) increase while a decrease is seen in high density lipoprotein cholesterol (HDL) and HDL_2 cholesterol. This effect is independent of age, body mass index (BMI) and other confounding variables.[4]

Women, however, differ from men as to the significance of these abnormal lipoproteins. In both men and women, CHD is increased with increasing LDL and total cholesterol levels. Hypertriglyceridaemia is, however, a more potent independent risk factor for CHD in women compared to men.[5] A meta-analysis of 17 studies (n = 46,413 men and 10,864 women) revealed that the CHD relative risk (RR) for hypertriglyceridaemia was elevated by 32% in men and 76% in women.[6] Low HDL is more predictive of coronary heart disease risk in older women than it is in men.[7]

3. Hypertension

Hypertension is an important risk factor for CVD in men and women. With Wong ***et al,*** based on an analysis of the NHANES data, calculated showed that control of hypertension to high normal levels would prevent approximately 20% of CHD events in men and 33% of CHD events in women.[8] If there was control to optimum levels, this would increase to 37% and 56% respectively. If hypertension, LDL cholesterol and HDL cholesterol were controlled to optimum levels, the same investigators showed that 82.1% of CHD events in women could be prevented.[9] A meta-analysis of data for 1 million men and women showed that for every 20 mm Hg difference in systolic blood pressure there is a 2 X difference in death rates due to stroke.[10] This is true in men and women.

4. Diabetes

It has been reported that diabetic women have a significantly higher cardiovascular mortality than diabetic men.[11] The relative risk of a fatal ischaemic heart event was 3.3 in diabetic vs non diabetic women and 1.8 in diabetic vs non-diabetic men. A similar difference has been reported by Hu ***et al*** who reported the relative risk for cardiovascular mortality in women with type II diabetes to be 4.4 as opposed to 2.2 in men.[12]

5. Obesity

Numerous population studies have shown an increased risk for CVD in overweight or obese men and women. In a Dutch prospective cohort study, it was estimated that 28% of CHD mortal-

ity could be attributed to being overweight (BMI > or = 25 kg/m^2).[13] In a 20 year follow-up of 15,402 obese men and women in Scotland, it was estimated that obesity in women was associated with 7 extra cardiovascular deaths and 28 extra cardiovascular admissions per 100 affected individuals.[14]

6. The Metabolic Syndrome

The metabolic syndrome is a clustering of risk conditions including dyslipidaemia (elevated TG, decreased HDL cholesterol), hypertension and abdominal obesity. Diagnosis in women requires the presence of 3 or more of the following:

1. Waist circumference > 88 cms)
2. Fasting TG ≥ 1.7 mmol/l (150 mg/dl)
3. HDL cholesterol < 1.1 mmol/l (50 mg/dl)
4. Hypertension (systolic blood pressure ≥ 130 mm Hg, diastolic blood pressure ≥ 85 mmHg, or use of antihypertensive drug therapy)
5. A fasting glucose measurement >or = 5.6mmol/l (100mg/dl).[15] Postmenopausal status is associated with a 60% increased risk of metabolic syndrome, even after adjusting for variables such as age, BMI or physical inactivity.[16] The metabolic syndrome appears to carry an especially high risk of CVD in women and it has been estimated that half of all cardiovascular events in women are related to this syndrome[17]

6. Smoking

For women smokers, CHD mortality risk from cigarettes is equivalent to the risk associated with weighing 42 kg more than her non smoking counterpart.[18]

The role of estrogen in the prevention of cardiovascular disease

The increase in the incidence of cardiovascular disease with onset of menopause at any age suggests a protective effect of estrogen on the vasculature. This is biologically plausible given the effect of estrogen on many surrogate markers of CVD. Oral estrogen, given alone or in combination with a progestin, improves lipoprotein profiles and lowers fibrinogen levels.[19] Both oral and transdermal estrogen improve glucose metabolism, have a beneficial effect on the vascular endothelium and reduce homocysteine levels. Other beneficial effects include a reduction of lipoprotein (a) levels.[20] The addition of a progestin partly attenuates the beneficial effect on lipoproteins. This effect varies according to the dose and androgenicity of the progestin. However, not all of the effects of estrogen are beneficial. Oral estrogen increases triglyceride levels. Oral estrogen also increases levels of C-reactive protein, an inflammatory marker that may independently increase the risk of heart disease.[21] This increase is not apparent with transdermal hormone therapy. The production of matrix metalloproteinases are increased by oral estrogen.[22] These are degradative enzymes that are important in destabilisation and rupture of plaque.

Observational studies have suggested that menopausal hormone therapy may prevent CHD. The most compelling is the Nurses Health Study (NHS), a 20 year prospective observational study. Among 70,533 participants with no history of cardiovascular disease, current use of HT, as compared with it never having been used was associated with RR of 0.61 (95% CI, 0.52 - 0.71) for a major cardiac event.[23] In the Rancho Bernado study, in a cohort of 204 postmenopausal women, current estrogen users had a 60% decreased risk of severe coronary artery disease (RR 0.40 [95% CI 0.19 - 0.82]).[24]

The suggested benefit of estrogen therapy on cardiovascular mortality has, however, not been confirmed by prospective randomised controlled trials. The Heart and Estrogen/Progestin Replacement Study (HERS), a secondary prevention study, compared the effect of conjugated equine estrogen (CEE) combined with medroxyprogesterone acetate (MPA), with placebo. It showed no reduction in the incidence of any cardiovascular outcomes over 4.1 years in those patients using CEE and MPA.[25] In the first year of this study, there was a 50% higher risk of non-fatal myocardial infarction in the group receiving HT. There was a decreased risk in years 3 to 5. This lower rate did not, however, persist during a 2.7 year follow-up of the HERS patients leading to the conclusion that postmenopausal hormone therapy should not be used to reduce the risk of CHD events in women with CHD.[26] This is consistent with other studies on secondary prevention and has been shown with both CEE and 17ß estradiol.[27, 28] There was also no protective effect in a secondary prevention study using transdermal estrogen.[29]

The Women's Heath Initiative (WHI) study was designed to address the issue of primary prevention. There were two parallel arms in a study on more than 26,000 women.[30, 31] The CEE plus progestin part of the study was stopped after 5.2 years because of risks outweighing benefits. At that stage there was an overall 24% increase in the incidence of CHD (nominal 95% CI 1.00 - 1.54).[32] As in the HERS study, this was most apparent at 1 year (RR 1.81 [95% CI 1.09 - 3.01]) with a trend toward a decreasing risk thereafter. The estrogen only arm of the WHI study also ended early (6.8 years) and again did not show any decrease in cardiovascular risk (RR 0.95 [95% CI 0.79 - 1.16]). Unlike the combined arm, there was no increase in risk in year 1 (RR 1.11 [95% CI 0.64 - 1.94]) and no significant trend with time.

Stroke risk with hormone use was increased and similar in both arms of the WHI study. The RR for stroke in the estrogen plus progestin arm was 1.31 (95% CI 1.02 - 1.68) and in the estrogen only arm 1.37 (95% CI 1.09 - 1.73).

The difference between the results of observational studies and the randomised controlled studies has attracted much comment. Manson provides an insightful overview of these issues.[33] Observational studies may be biased due to a "healthy user effect", i.e. women who choose to take HT tend to be healthier and tend to adopt other health promoting interventions. If this was the situation for the WHI studies it is therefore strange that, with other endpoints of this study such as venous thrombosis, stroke and breast cancer, the results were in accordance with the observational studies. Observational studies can also be compromised because, due to infrequent capture of adverse events, early clinical events may be misinterpreted as occurring in a non-user or in a non-using interval. This could be especially important in studies on CHD outcomes where, as shown in WHI and HERS, most events occur early in the study. An extremely important difference is, however, the difference in the clinical characteristics of the study populations. In observational studies such as the NHS study, the majority of the participants started hormone therapy (HT) early in the menopause. This is not the case in WHI and HERS studies where the mean baseline ages were 63 and 67 years respectively. At this older age, the majority of women

would be expected to have a degree of atherosclerosis. This obvious difference has lead to a "window of opportunity" hypothesis where HT may be of benefit in the younger patient with healthy vasculature, whereas, in the older patient, initiating HT for the first time, where vascular damage has already occurred, HT would be detrimental. The results as regards the incidence of CVD in the estrogen only arm of the WHI lends support to this hypothesis.[34] When looking at the primary outcome of myocardial infarction (MI) and coronary death, the risk for developing one of these events with use of estrogen therapy increased with age. In the age groups 50 - 59 years, 60 - 69 years and 70 -79 years, the RR's were 0.61 (95% CI, 0.25 - 1.50), 0.86 (95% CI, 0.60 - 1.25), and 1.10 (95% CI, 0.69 - 1.73). As regards the composite outcome of MI, coronary death, coronary revascularisation and angina, there was a significant reduction with use of estrogen in the 50 - 59 year age group (RR 0.66 [95% CI, 0.45 - 0.96]). There was no difference in composite outcomes in the 60 - 69 or 70 - 79 year age groups. A re-analysis of the NHS data looking at age again shows benefit with initiating HT early in menopause with no benefit in women starting HT at a later stage.[35] Where HT was initiated near menopause, the RR of CHD for estrogen use alone was 0.66 (95% CI, 0.54 - 0.92) and for estrogen/progestin use was 0.72 (95% CI, 0.56 - 0.92). Where HT was initiated more than 10 years after menopause, the RR for estrogen and estrogen/progestin use were 0.87 (95% CI, 0.69 - 1.10) and 0.90 (95% CI, 0.62 - 1.29) respectively.

Nonhuman primate studies also support the window of opportunity hypothesis. Where CEE, with or without MPA, was started in cynomolgus monkeys immediately after oophorectomy, there was a reduction in the extent of plaque formation due to atherosclerosis.[36] If the HT was delayed by 2 years, which is equivalent to 6 human years, there was no effect on plaque development.

The debate about the role of HT in the prevention of CVD in postmenopausal women will continue until there are prospective randomised controlled studies that address this issue in recently menopausal women. The Kronos Early Prevention Study (KEEPS) is one of these studies.[37] It may also shed light on the issue as to whether there is a difference between oral or transdermal estrogen as regards cardiovascular disease. Until we have Level I evidence that HT protects menopausal women against CVD it should not be prescribed where this is the only indication.

The prevention of heart disease in women should, therefore, be based on proven interventions. At present there is no evidence for the efficacy of aspirin in the prevention of myocardial infarction or cardiovascular death in women. The Women's Health Study, a 10 year prospective study of 39,876 healthy women aged 45 years or older, showed the relative risk for major cardiovascular events with aspirin use to be 0.91 (95% CI, 0.80 - 1.03).[38] Ischaemic strokes were, however, significantly decreased (RR 0.76 [95% CI, 0.63 - 0.93]). A recent meta-analysis confirmed that statins

have proven benefit in decreasing CHD mortality in patients with coronary heart disease.[39] The issue as regards primary prevention in women is not as clear. In the same meta-analysis, although CHD events were decreased, there was no decrease in CHD or total mortality in patients without CHD. However, current guidelines for cardiovascular disease prevention emphasise the importance of achieving recommended lipoprotein goals.[40]

As discussed under risk factors for CVD in women, there is evidence for cardiovascular compromise caused by dyslipidaemias, hypertension, diabetes, obesity, the metabolic syndrome and smoking. Treatments and lifestyle interventions to address these problems should form an integral part of prevention programmes in menopausal women. Considering the morbidity and mortality of cardiovascular events, a paradigm shift away from the hot flush discussion, PAP smear and breast examination focus of the "regular check" in menopausal women, towards a disease prevention strategy with focus on other risk factors such as those for cardiovascular disease, would have far reaching health benefits for women.

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This article has been peer reviewed

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