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A Systematic Review on Risk Factors Based on Gender and Management of Coronary Heart Disease

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ABSTRACT

Over the past years it has been recognized that women are more susceptible to coronary heart disease than men and it should be acknowledged in the management and assessment of coronary heart disease. Then there is a remarkable progress in the knowledge of cardiovascular risk factors related to gender. Triglycerides, high density lipoproteins levels, diabetes have been found to have greater Influence on coronary heart disease in women than men. But certain evidence showing that lipoprotein is a stronger cardiovascular risk factor in men compared to women. Risk factor control in patient with CHD remains poor, especially for obesity, smoking, and blood pressure in spite of guidelines. Patient should initiate or maintain lifestyle modification- weight control, increased physical activity, moderation of alcohol intake, limited sodium consumption, maintenance of a diet high in fresh fruits, low fat dairy products etc. Long acting drugs also minimize blood pressure variability and this may offer protection against progression of target organ damage and cardiovascular events. This review article addresses the impact of cardiovascular risk factors on both men and women and management of coronary heart disease.

Keywords: Diabetes, HDL and Triglycerides

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INTRODUCTION

Coronary heart disease (CHD) remains one of the leading causes of death. CHD is the accumulation of plaque in the arteries of the heart that supply the blood for maintaining normal cardiac function. The accumulation of plaque narrows the heart's arteries and reduces the blood flow results ischemia of myocardial tissues with deterioration of heart function. CHD also caused the deposition of fat beneath the endothelium thereby reduces elasticity of arteries. The major risk, factors including hypertension, hypercholesterolemia, diabetes, smoking etc. There are a number of lifestyle modification that can be implemented to improve the prognosis of patient with CHD including smoking cessation, adoption of a Mediterranean diet, body weight reduction and increased physical activity. Current treatment option for stable CHD involved antianginal treatment to improve symptoms and quality of life along with a cardio protective treatment to prevent cardiovascular events. As per Joint National Conference VII guidelines, blood pressure, 140/90 mmHg, or, 130/80 mmHg for patients with diabetes or chronic kidney disease, is recommended. Dietary therapy should include reduced intake of saturated fats (to, 7% of total calories), trans fatty acids, and cholesterol. Daily physical activity and weight management are recommended. Statin therapy should always be preferred for patients with established CHD, based on the benefits in the reduction of the risk of atherosclerotic complications. Physical activity should be encouraged, involves increases exercise tolerance, reduces symptoms of angina, and reduction in weight, blood lipids, blood pressure, glucose tolerance, and insulin sensitivity. All patients should be encouraged to do 30–60 min of moderate-intensity aerobic activity, such as brisk walking etc. Patients should be advised to take a 'Mediterranean' diet, with vegetables, fruit, fish, and poultry. Body mass index and waist circumference should be assessed regularly. Diabetes management should include lifestyle and pharmacotherapy measures to achieve a near-normal HbA1c. In type 1 diabetes, glycemic control requires appropriate insulin therapy and concomitant dietary therapy. In type 2 diabetes, professional dietary advice, weight reduction, and increased physical activity should be the first treatment, followed by pharmacological treatment (oral hypoglycemic treatment and insulin when needed) aiming at good glucose control and psychological risk factors should also be controlled such as excessive anxiety or depression. The pharmacological treatment for CHD including Antiplatelet agents, lipid lowering drugs, ACE inhibitors, beta blockers, Calcium channel blockers, nicorandil and myocardial revascularization.

Epidemiology

CHD is the leading cause of death worldwide and the lifetime risk of developing CHD at age 40 years is 50% accounts for men and 33% for women. Most studies shows that the change in mortality was similar for both men and women.

Table 1 Risk factors for men and women

Risk factor	Men	Women
Total cholesterol	+++	+++
LDL	+++	+++
HDL	++	+++
Triglycerides	+	++
Apo A-I	+++	+++
Apo-B	+++	+++
Apo(a)	++	+(+)
Smoking	++	++(+)
Diabetes	++	+++
Obesity		
BMI	++	++
WHR	+++	+++
Hypertension	++	++
Family History	++	++(+)
Hormones		+++
12	+	+
Fibrinogen	++	++
Inflammation (CRP)	+	++
Infection (HP, ChP)	–	–
Psychosocial factors	+	+

RISK FACTORS

1) High-density lipoprotein cholesterol

High-density cholesterol (HDL) levels are closely and inversely related with the risk of CHD. HDL levels are higher in women than in men from young adulthood onwards. Certain studies shows that there is a decrease in HDL levels following the menopause. The loss of protection against HDL is a major factor for the increased coronary risk in postmenopausal women. It has been suggested that low levels of HDL are more predictive of coronary artery disease in women than in men. Because of the higher level of HDL in women, an alteration of the current National Cholesterol Education Program (NCEP) guidelines has been proposed with more aggressive targets for HDL in women. Although low level of HDL has no risk in the absence of elevated LDL cholesterol, total cholesterol or elevated triglyceride levels, several studies have recently shown that an ‘isolated low HDL’ level represents a significant risk of CHD. The Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) showed that a modest increase in HDL

levels in men with CHD and normal LDL levels (≤3.6 mmol/l) resulted in a significant reduction in the risk of major cardiovascular events and similar data for women are not available In conclusion, the HDL level is an important factor affecting atherosclerosis. It might be appropriate to apply a gender based approach in interpreting HDL levels because of the higher absolute levels and possible greater impact of HDL in women.

2) Triglycerides

Elevated levels of triglycerides have been associated with an increased risk of CHD in both men and women. However, the role of plasma triglycerides as an independent risk factor is still difficult to describe. But there are methodological difficulties in interpreting triglyceride levels because of high biologic intra- and inter-individual variability and strong interactions exist between triglycerides and other lipid factors. Elevated triglycerides are often seen with lower HDL levels and this combination has been associated with increased CHD risk. A meta-analysis including more than 46000 men and nearly 11000 women showed for men and women, respectively, a 32 and 76% increase in cardiovascular risk associated with a 1-mmol/l increase in triglycerides. After adjustment for HDL and other risk factors, these risks were decreased to 14% in men and 37% in women, but this remained statistically significant for both genders. It describes that elevated triglycerides increase cardiovascular risk more in women than in men, indicating a gender difference in the role of triglycerides in atherosclerosis. Therefore, similar to the gender-specific approach for HDL, the latest NCEP guidelines have suggested that the optimal levels for triglycerides may be lower for women. There is a strong evidence that postprandial triglyceride levels are of major importance in determining cardiovascular risk and that premenopausal women have lower triglyceride levels than men and postmenopausal women.

3) Apolipoproteins A-I and B

Apolipoprotein A-I (apo A-I) is the major apolipoprotein of HDL and has previously been reported to be a better marker for CHD than HDL. Biologically, this finding is plausible because not all HDL particles are equal in size. Two subclasses of HDL can be recognized, HDL particles that only contain apo A-I, lipoprotein A-I, and particles that contain both apo A-I and apo A-II, lipoprotein A-I/A-II. In general, lipoprotein A-I is considered to be more protective against CHD than lipoprotein AI/A-II. Therefore, apo A-I levels may be a better marker for functional reverse cholesterol transport than HDL. Because HDL appears to be a less adequate predictor for CHD for men than women, apo A-I measurement might be particularly valuable for men.

Atherogenic lipoproteins including LDL particles, very low density lipoprotein (VLDL) particles, and remnants of triglyceride-rich particles each contain one molecule of apo B. Consequently, apo

B suggest an accurate estimation of the total number of atherogenic particles. The composition of LDL particles, each containing one molecule of apo B, is heterogeneous because of the variable content of cholesterol. Smaller and denser LDL particles are more atherogenic than larger one. Therefore, apo B could be superior compared to LDL in determining CHD risk. In conclusion, both apo A-1 and apo B might be better predictors for CHD in both men and women and more suitable for cardiovascular risk assessment than traditional lipid factors.

4) Lipoprotein

Lipoprotein consists of an LDL particle bound by a disulfide bridge to apolipoprotein and has a structure resembling plasminogen. Lipoprotein levels are independent of other lipid parameters. In women, circulating lipoprotein levels increase after the menopause just like the other lipid parameters like triglycerides, LDL and total cholesterol.

Most cross-sectional, case-control studies and prospective studies shows that lipoprotein is a risk factor for CHD. Prospective studies have reported that elevated levels of lipoprotein that is >0.30 g/l are associated with an increase in CHD in men and women. Other data indicate that lipoprotein is not a strong risk factor for CHD in women as in men. Elevated lipoprotein levels are difficult to treat. The only drugs that lower lipoprotein levels are nicotinic acid and hormone replacement therapy (HRT) In conclusion, lipoprotein can be regarded as a cardiovascular risk factor, but the evidence in women is not as strong as in men. More data are necessary to determine whether gender-related differences are clinically relevant.

5) Smoking

Smoking is the most important preventable cause for the development of CHD in both men and women. In United States 23.9% of women and 27.3% of men older than 18 years are current smokers. A clear dose–response relationship exists between the number of cigarettes smoked and the increase of risk of CHD. Smoking cessation can be reduce the risk of CHD in both genders.

A number of studies showed that smoking is a stronger risk factor for myocardial infarction in middle-aged women than in men. Smoking has also been associated with an early menopause. A recent study showed that current smoking decreased the age of the natural menopause by 2 years and past smoking by 1 year. In both men and women smoking has an unwanted effect on plasma lipoproteins and decrease in HDL. Some studies have suggested that this harmful effect on HDL is more in female smokers than in male smokers. In conclusion, smoking is a very important modifiable risk factor that have at least a similar impact in both women and men.

6) Total cholesterol and low-density lipoprotein cholesterol

Total cholesterol and low-density lipoprotein cholesterol (LDL) levels in men and women are similar up to ~20 years of age and cholesterol levels increase more sharply in men than in women. Total cholesterol and LDL levels in women even exceed the levels in men following the menopause. Estrogens are potent LDL receptor-upregulating agents and in the presence of low endogenous estrogen levels, LDL receptor activity is reduced. This leads to elevated LDL concentration in postmenopausal women. Elevated total cholesterol and LDL levels are major risk factors for CHD in both men and women. Recent studies included a sufficient number of women to show that they respond at least as well as men to cholesterol lowering therapy. The Scandinavian Simvastatin Survival Study showed that a reduction of high cholesterol level (range 5.5–8.0 mmol/l) in patients with CHD reduced major coronary events by 34% in both men and women. In the Cholesterol and Recurrent Events (CARE) trial, which described the effect of pravastatin in patients with average cholesterol levels (6.2 mmol/l), women had a risk reduction of major coronary events which was twice as large as that in men.

7) Hypertension

Elevated systolic blood pressure is a risk factor and powerful as diastolic blood pressure. Isolated systolic hypertension, defined as a systolic blood pressure ≥160 mmHg and a diastolic blood pressure <90 mm Hgis associated with an increased risk of cardiovascular disease, stroke and all-cause of mortality in both men and women. Isolated systolic hypertension is an indication of loss of arterial elasticity, and its prevalence increases with age for both sexes. However, the elevation in prevalence of isolated systolic hypertension is steeper for women than for men ≥55 years of age. Isolated systolic hypertension is a common finding in elderly women, with a prevalence of 30% in women over 65 years of age. The Systolic Hypertension in the Elderly Program (SHEP) has shown that both men and women with isolated systolic hypertension benefit from blood pressure control. Antihypertensive treatment reduces the incidence of stroke and non-fatal myocardial infarction. Large long-term clinical trials have included both men and women and a meta-analysis of these studies did not show significant gender differences in blood pressure and clinical outcome. The current guidelines suggest that antihypertensive therapy for a heterogeneous population including pregnant women or women on oral contraceptives, elderly individuals and persons with isolated hypertension. In conclusion, hypertension is a highly prevalent risk factor and an important marker for patients with a high-risk profile.

8) Obesity

Obesity is an independent risk factor for CHD in women compared to men. Independent of overall obesity, the distribution of body fat is an indication of cardiovascular risk. Waist-hip ratio and waist

circumference are highly correlated to the risk of CHD. Weight reduction was associated with an improvement in risk factors and changes in triglycerides, high and low-density lipoprotein levels and blood pressure. These observations suggest a beneficial effect of weight reduction, but there is no direct evidence available that weight loss reduces the risk of CHD Because of the difficulty of achieving and maintaining weight loss, the prevention of obesity is important.

9) Family history

Family history shows that a strong relationship with cardiovascular risk factor and which is complicated by methodological factors such as identification and the definition of a positive family history and endpoints. These factors can act as confounding elements in comparing study results and the interaction between known risk factors and family history is evident. Therefore, the underlying mechanism of how family history acts as a risk factor and the separate impact of genetic and environmental factors is still controversial. Several studies showed that a parental history of CHD increases the chance of premature onset of CHD in men. An early study showed that an independent effect on cardiovascular death was only present in men of <60 years but not in women. This study however did not include a sufficient enough number of women to detect a significant relationship between family history and risk of CHD. More recent studies have reported that a family history of CHD is also a risk factor for women. Some recent studies showed that the risk of premature CHD was higher in women compared to men. A Finnish study showed that 76% of the women and 62% of the men who survived a myocardial infarction had first degree relatives with CHD at <65 years of age history as a risk factor are uncertain.

In conclusion, women and men with a positive family history have an increased risk of premature coronary events. Recent results indicated that this risk might be higher in women compared to men. Neither the evaluation nor the interpretation of family history as a risk factor for CHD are completely established.

10) Fibrinogen

The haemostatic system plays an important role in the pathogenesis of atherosclerosis. Several studies have shows that a significant association of fibrinogen level and cardiovascular disease in both men and women. Plasma fibrinogen levels are higher in women and increase with smoking, age, post-menopausal status, obesity and use of oral contraceptives. Smoking cessation, alcohol use and weight loss have a lowering effect on fibrinogen levels. In the Framingham study, the risk for CHD associated with fibrinogen diminished with age in women but not in men. After the menopause, the levels of fibrinogen increase, but as antithrombotic factors like antithrombin III and plasminogen increase, the net effect of the menopause is unclear. Several drugs including fibrates, propranolol,

nislodipine and ticlopidine and HRT have been reported to lower fibinogen levels. In conclusion, fibrinogen is an important cardiovascular risk factor that can be modified by external factors (e.g. drug therapy), life style and the female hormonal status.

11) Infections

The possible role of chronic infections and CHD has been investigated in a number of studies. Most of these studies relate to *Helicobacter pylori* and *Chlamydia pneumoniae*. A large number of studies found evidence for an association between *C. pneumoniae* antibodies and CHD. Two studies carried out a separate analysis for men and women. One study found a possible association between circulating *C. pneumoniae* DNA and CHD in men only and the other study found that serological evidence of an *C. pneumoniae* infection was associated with an atherogenic lipid profile in men but not in women. None of these prospective studies found any statistically significant evidence for a relationship between CHD and *H. pylori* infection. In summary, data are not available to show that infective agents are of major importance as risk factors for CHD in either men or women.

12) Inflammation

Inflammation as assessed by C-reactive protein (CRP) levels has been demonstrated to predict cardiovascular events in healthy middle-aged and elderlymen. Recently, the predictive value of CRP has been investigated in middle-aged and elderly women and both studies found that the relative risks associated with CRP were higher for women than for men. In a recent study, Ridker et al. raised the possibility of adding CRP measurements to the standard lipid screening, since CRP was the most significant and strongest risk factor for cardiovascular events in healthy middle-aged women compared to measurements of lipids and apolipoproteins. In conclusion, evidence of the importance of CRP as marker for future CHD is becoming more convincing for women.

13) Psychosocial factors

Psychosocial factors such as socio-economic status and social support have been strongly associated with CHD in both men and women. Several studies have demonstrate the role of psychosocial issues for women. A low education level has been associated with an increased incidence of CHD. The psychosocial work environment also seems predictive for future CHD. The Whitehall II study showed that men and women with low job control, either self-reported or independently assessed, had a higher risk of newly diagnosed CHD. Subjects with low job control had an odds ratio for any subsequent coronary event of 1.93 compared to subjects with high job control. This association could not be explained on the basis of employment grade or classic coronary risk factors In conclusion, these findings support the significance of psychosocial factors for CHD for both men and women.

14) Estrogens

In comparison with men of a similar age and postmenopausal women, the incidence of CHD is significantly lower in premenopausal women suggesting that endogenous estrogens have a protective effect on the development of CHD. Estrogens affect the atherosclerotic process through a variety of mechanisms and have a lowering effect on total cholesterol, LDL and lipoprotein levels. HDL levels are increased and postprandial lipid metabolism improved by estrogens. Moreover estrogens have an acute vasodilatory effect on the vessel wall and an athero protective effect involving inhibition of smooth-muscle cell proliferation. The role of exogenous estrogens is controversial. Meta-analyses of multiple observational studies suggested a 35–50% reduction of CHD associated with the use of estrogens after the menopause. The Hormone Estrogen Replacement Study (HERS) which compared HRT consisting of estrogen plus progestin with placebo in women with CHD showed no overall benefit of HRT on coronary death and non-fatal myocardial infarction. An increase was seen in the relative risk of venous thrombotic events and gallbladder disease of 2.89 and 1.38, respectively. No effect was found for estrogen alone or estrogen in combination with progesterone on the progression of coronary atherosclerosis. Estrogen therapy might be more protective in preventing atherosclerosis than in slowing down the progression of established disease. No data for estrogen therapy in primary prevention are currently available. A new therapeutic approach is the use of Selective Estrogen Receptor Modulators (SERMs), non-hormonal agents which share the effects of estrogen that are favorable on bone and the cardiovascular system but not in other tissues such as the breast and endometrium. In healthy menopausal women raloxifen had a favorable effect on cardiovascular risk by decreasing LDL, fibrinogen and lipoprotein levels.

PHARMACOLOGAL TREATMENT

Anti-Platelet Agents

The anti-platelet agents like Aspirin irreversibly inhibits cyclooxygenase enzyme and, reduces the synthesis of thromboxane. For the prevention of arterial thrombosis, chronic low dose (75–150 mg/day) can be used. The antiplatelet agents clopidogrel and ticlopidine are more expensive than aspirin, but have a similar overall safety profile and may be good options in cases of aspirin intolerance (e.g. patients with bronchospasm).They have antithrombotic effects comparable to those of aspirin. High-risk patients may benefit from combination of aspirin with an anticoagulant agent such as warfarin. However, unless there is a specific separate indication, anticoagulants should be avoided in stable CAD.

Lipid Lowering Agents

There is a strong association between increased low density lipoprotein (LDL) cholesterol levels and the risk of CVD. The Heart Protection Study clearly demonstrated that lipid-lowering treatment was beneficial in patients with a history of CAD, and such therapy should be an integral part of the management of all CAD patients. Statins have been reported to decrease cardiovascular complications by up to 30%, even in the elderly and patients with diabetes. It is known that the deleterious effects of serum cholesterol begin at low-normal levels, and pre-treatment cholesterol level does not determine the benefits of long-term statin therapy; treatment is therefore useful in patients with normal cholesterol levels but high cardiovascular risk. This explains why it is currently recommended to treat patients at high cardiovascular risk with a statin, even if they have normal or near-normal LDL cholesterol levels.

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are widely used in the treatment of hypertension and heart failure. Trials in patients with heart failure and post-MI reported reduced cardiac mortality and MI with ACE inhibition, which ultimately led to the investigation of the role of these agents in secondary prevention for CAD patients without heart failure. In the European trial of Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA), there was a20% relative risk reduction in the composite primary end point of cardiovascular death, MI, or resuscitated cardiac arrest in the perindopril treatment group. Results in favour of ACE inhibition also came from the Heart Outcomes Prevention Evaluation (HOPE) study with Ramipril, in which there was a 22% reduction in the composite primary endpoint of cardiovascular death, MI, and stroke. The conclusion drawn from these studies is that ACE inhibition with perindopril or Ramipril could have additional cardiovascular effects via mechanisms other than reduction of blood pressure. Secondary prevention with ACE inhibition is therefore recommended for patients with proved CAD if they have had a previous MI, or have diabetes, concomitant hypertension, heart failure, or asymptomatic LV dysfunction.

Beta-Blockers

Beta-blockers can reduce the risk of cardiovascular death or MI by about 30% in post-MI populations. Beta-blockers are currently recommended in such patients, and in patients with heart failure. Beta-blockers reduce HR at rest and during exercise, and are the standard choice for the symptomatic treatment of stable angina and ischaemia, provided the agent is initiated carefully and titrated progressively to full dose to achieve resting HR less than 60 b.p.m.55 Up titration of beta-blockers might be limited by side effects, such as fatigue, depression, lethargy, insomnia, nightmares, and worsening claudication.

I_F Current Inhibitor Ivabradine

I_f current atenolol resulted in a significant reduction in HR and improvement in all parameters of exercise capacity. I_f current inhibitor ivabradine selectively inhibits the I_f cardiac pacemaker current, thus exerting selective HR reduction while preserving LV contractility and relaxation. It provides powerful anti-ischaemic and anti-anginal efficacy in patients with stable angina. The recent ASSOCIATE study clearly demonstrated that treatment with ivabradine in patients with stable angina receiving the beta-blocker atenolol resulted in a significant reduction in HR and improvement in all parameters of exercise capacity. The results of the BEAUTIFUL study suggest that ivabradine has the ability to affect not only symptoms of myocardial ischaemia, but also potentially to improve coronary outcomes in patients with elevated HR (≥70 b.p.m.), which makes it an interesting agent for the management of patients with CAD.

Calcium Channel Blockers

Calcium channel blockers (CCBs), through selective inhibition of the L-type calcium channels, lead to dilation of the coronary and other arteries, which decreases cardiac work and counteracts vasospasm. The non-dihydropyridine CCBs (e.g. verapamil and diltiazem) reduce HR, myocardial contractility, and atrioventricular nodal conduction. Calcium channel blockers reduce the frequency and sever it yofanginal attacks, but there is no evidence supporting their use to improve prognosis in stable CAD patients. ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system) found no benefit of nifedipine over placebo in stable angina in terms of composite endpoints, including death, MI, refractory angina, and heart failure.

Nicorandil

Nicorandil is a potassium channel opener with a nitrate like effect. The IONA (Impact Of Nicorandil in Angina)study showed fewer major coronary events in patients treated with nicorandil vs. placebo, but significance was driven mainly by a reduction in 'hospital admission for cardiac chest pain'. The risk of death and non-fatal MI was unaffected.

Myocardial Revascularization

Revascularization includes either PCI, usually with stent implantation, or coronary artery bypass graft (CABG) surgery. The results of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, showed no benefit in terms of all-cause mortality, MI, or other major cardiovascular events of adding PCI in stable CAD patients receiving optimized medical therapy. Moreover, the marginal quality of life benefit obtained by revascularization in that trial had completely disappeared after 3 years. A remarkable finding from COURAGE is that the majority of patients had substantial improvements in health status (with contemporary treatment)

that were sustained for several years. At the same time, the rapid improvement with optimal medical therapy alone suggests that antianginal medications are underused in practice. The COURAGE trial redefines the contemporary roles of optimal medical therapy and PCI in the management of patients with stable CAD. It suggests the complementary role of optimal medical therapy as first-line therapy, with PCI reserved for patients who do not respond or who have severe symptoms. In some circumstances, for example in patients with severe lesions in coronary arteries that supply a large area of the myocardium, revascularization can improve prognosis by increasing the effectiveness of the existing perfusion or providing alternative routes of perfusion. Whatever the decision to revascularize or not the patient should be advised that secondary preventative pharmacological therapy will continue to be necessary, even after the intervention. The risks and benefits of surgery or PCI should also be carefully discussed with the patient.

CONCLUSSION

In this review an update is provided on the role of a number of risk factors with emphasis on possible differences between men and women. Except for female hormonal status, no risk factor has been recognized as acting on one gender but not on the other. This finding indicates that the pathogenesis of CHD is very similar for men and women. Yet, diabetes, HDL and triglycerides levels have been found to have a greater impact on CHD risk in women compared to men. In addition, there are indications that risk factors such as smoking, family history and inflammation characterized as C-reactive protein, have a more negative influence on CHD in women than in men. On the other hand the evidence showing that lipoprotein is a cardiovascular risk factor seems to be stronger in men than in women. The majority of cardiovascular risk factors show no important differences between the genders.

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