
An alternative hypothesis explaining gender differences in the risk of coronary heart disease

AKTUELT PROBLEM

KAARE HARALD BØNAA

kbonaa@hotmail.com

Department of Cardiology

St Olav's Hospital, Trondheim University and

Department of Community Medicine

University of Tromsø

One of the most striking features of the epidemiology of myocardial infarction is the gender difference: compared with men of the same age, women have a lower lifetime risk of myocardial infarction but appear to be less well protected against angina pectoris. There is no evidence from epidemiological studies or controlled clinical trials that oestrogen is the protective factor for women. This paper proposes an alternative hypothesis: men have a higher risk than women of coronary death and myocardial infarction because they are more likely to develop lipid-rich, unstable and thrombogenic atherosclerotic plaques in the coronary arteries. This may be attributable to gender differences in HDL cholesterol levels, which are impacted by testosterone. The proposed hypothesis is consistent with epidemiological observations and experimental findings, and is also in line with current understanding of the pathophysiological mechanisms underlying atherosclerosis and coronary heart disease.

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It is well established that women have a substantially lower risk than men of myocardial infarction or coronary death, although the reason is unknown (2). This is somewhat surprising, as the gender difference in the risk of coronary heart disease is one of the most striking features of the disease's epidemiology, and few chronic

diseases have been the subject of such intensive research as coronary heart disease. The following two statements are frequently cited in both the scientific literature and medical textbooks:

- Women are protected against coronary heart disease until menopause, i.e. around the age of 50; thereafter, the risk increases rapidly, whereby older women have the same – or even higher – risk compared with older men.
- Use of hormone therapy with oestrogen in postmenopausal women protects against cardiovascular disease.
- Neither of these statements is scientifically substantiated. It is a myth that menopause leads to a marked change in women's risk of coronary heart disease (3–5), and there is no evidence that oestrogen supplementation reduces the risk (6, 7).

However, if neither menopause (cessation of endogenous oestrogen production) nor oestrogen supplementation impacts on women's risk of coronary heart disease, what is it that protects them? The aim of this paper is to present a range of epidemiological and pathophysiological observations that form the basis for proposing an alternative explanation for the gender differences in coronary heart disease.

Coronary heart disease mortality

Table 1 shows coronary heart disease mortality (ICD-10: I20–I25) in Norway in the period 1996–98. The table is based on data from the National Health Screening Service (8). An average of 4712 men and 3899 women aged over 25 years died each year from coronary heart disease. Mortality increases markedly with age in both sexes, and the mortality rate is higher in men than in women in all age groups. In the oldest age groups, the number of women dying from coronary heart disease is higher than for men, but this is because there are more women in these age groups, as women live longer than men. The absolute difference in rates, i.e. excess mortality from coronary heart disease in men compared with women, increases continuously with age and is greatest in those over the age of 80. There is therefore no evidence in Table 1 that women's protection against coronary heart disease diminishes after menopause. On the contrary, it is only after menopause that this protection becomes truly apparent in the statistics.

Table 1 and corresponding data from other countries (3–5) show that, in women, there is a continuous age-related increase in the risk of coronary heart disease. The perimenopausal period (in Norway and other Western countries the average age at menopause is approximately 50 years) does not represent any deviation from this age trend. Other studies in larger Western populations, which provide more stable estimates than Norwegian statistics, show that the risk of coronary heart disease in women increases by a factor of approximately 2.3 per five-year age group from the age of 20 to old age (3, 5). When women's mortality is plotted on a logarithmic scale, the increase in risk per five-year age group is found to be approximately linear between the ages of 20 and 90. This means that the proportional increase in risk between five-year age groups is constant.

In men, however, the pattern is different. Mortality increases in younger men by a factor of approximately 3.5 per five-year age group, whereas in older men the increase is approximately 1.5 per five-year age group. On a logarithmic scale, the mortality curve for men is therefore concave and gradually approaches that of women, but the curves never intersect (3, 5). The curves draw closer because the rate of increase (acceleration) in mortality declines in older men, while remaining constant in women.

In contrast to coronary heart disease, breast cancer – a well-known oestrogen-dependent disease – shows a clear deviation in the age-related trend at around 50 years of age (4).

Other types of analyses have also been unable to demonstrate that menopause represents a risk factor for coronary heart disease in women. In multivariate statistical analyses that include risk factors such as cholesterol, blood pressure, smoking, age, etc. to explain the incidence of myocardial infarction in women, the menopause variable does not make an independent contribution to the explained variance.

In all age groups, mortality from coronary heart disease is therefore lower in women than in men. This gender difference is observed consistently across regional variations in the incidence of coronary heart disease.

Angina pectoris and myocardial infarction

A number of studies have shown that the gender difference in the prevalence of angina pectoris is much smaller than for myocardial infarction (9). This finding is striking, yet it has received relatively little attention. In connection with the Tromsø population survey in 1994–95, in which more than 75 % of the population participated, 27,000 women and men were asked whether they had, or had ever had, symptoms of angina pectoris and whether they had experienced myocardial infarction. The results are shown in Table 2. For myocardial infarction, the age pattern and gender difference are the same as for coronary mortality. In total, 4.1 % of men and 1.6 % of women reported a history of myocardial infarction. In all age groups, the proportion is higher in men than in women: even among those over 80 years of age, more than twice as many men reported such a history.

The picture for angina pectoris, however, is quite different (Table 2). Overall, an equal proportion of women and men reported symptoms of angina pectoris (2.6 %). Up to the age of 70, more men than women reported angina pectoris, but the gender difference is smaller than for myocardial infarction. After the age of 70, the prevalence of angina pectoris is fairly similar in both sexes: among the elderly, a slightly higher proportion of women than men actually report symptoms of angina pectoris. Similar findings have been reported in other studies, such as the large Copenhagen population study and the well-known Framingham Heart Study.

In the Framingham Heart Study, approximately 6000 men and women were examined every two years over a period of more than 30 years (9). For angina pectoris, the mean annual incidence of new cases at ages 35–64 was 3 % for women and 4 % for men. At ages 65–94, the incidence of angina was 6 % in both women and men. For myocardial infarction, the incidence at ages 35–64 was approximately 2 % in women and 6 % in men, and at ages 65–94 the incidence of myocardial infarction was 7 % in women and

15 % in men. Thus, the incidence of angina pectoris in older women was similar to that in men, but only half as many older women as men experienced myocardial infarction. Furthermore, the first clinical manifestation of coronary heart disease was usually angina pectoris in women and myocardial infarction in men. Women tended to present with stable angina pectoris, whereas in men it was more likely to be unstable angina pectoris progressing to myocardial infarction (9).

It may seem paradoxical that older women are better protected than older men against myocardial infarction but not angina pectoris, despite both conditions sharing the same underlying disease process (atherosclerosis). For many years it has been argued that this paradox may be explained by the fact that angina pectoris is more difficult to diagnose in women than in men, and that many women reporting exertional chest pain are found not to have coronary heart disease upon further investigation (e.g. coronary angiography). However, evidence supporting this is weak. It is true that exercise test results can be more difficult to interpret in women than in men, particularly among the elderly, but this may be a reflection of limitations in the diagnostic method. It is also possible that doctors have simply found it difficult to believe that women reporting exertional chest pain truly have coronary heart disease, given the relatively low incidence of myocardial infarction in women.

It has been argued that the symptoms of angina pectoris are often vague and non-specific, and that the validity of questionnaire surveys is low. This may be true, but there is no evidence that women's reporting of other conditions, such as diabetes, stroke, gastrointestinal diseases, etc., is less accurate than that of men. So why should this be the case for angina pectoris?

Let us, for the time being, assume that large-scale epidemiological population studies provide an accurate picture of reality, and that middle-aged and older women and men are equally affected by angina pectoris, but that women are less susceptible to myocardial infarction. What could the explanation be?

Pathophysiology of atherosclerosis and coronary heart disease

Atherosclerosis is by far the predominant cause of coronary heart disease (10). It is a pathological, chronic process and not an inevitable, normal consequence of ageing. Atherosclerosis begins early in life and affects large and medium-sized arteries, starting with the deposition of cholesterol-rich lipoproteins (primarily low-density lipoprotein – LDL) in the innermost layer of the arterial wall, the intima. Lipoproteins circulate in plasma, and endothelial cells, which line the inner surface of the vessel wall, are permeable to LDL, allowing a continuous transport of lipoproteins to and from the vessel wall. Cholesterol cannot be degraded within the vessel wall. Another lipoprotein (high-density lipoprotein – HDL) is responsible for transporting cholesterol from the vessel wall back to the liver, where it can be broken down and excreted.

According to the widely accepted response-to-injury hypothesis, there must be endothelial injury in the blood vessels before cholesterol deposition begins. Such injury increases permeability and can be caused by hypertension, smoking or inflammation. However, there is evidence that this hypothesis is not correct, and that cholesterol

deposition occurs without prior injury (11). Findings from animal models are consistent with a concentration-dependent transport of intact lipoprotein particles from the lumen through an intact endothelial cell layer into the intima.

Hypertension and smoking have an adverse effect on the development of atherosclerosis, but the mechanisms are not fully understood. The closest we come to a *sine qua non* for atherosclerosis, however, is a sufficiently elevated plasma cholesterol level. The exact biologically optimal cholesterol level in terms of protection against myocardial infarction is not known, but it is probably around 3 mmol/L. Such levels are rarely observed in adults in the Western world but are common among farmers in China, in which coronary heart disease is exceedingly rare.

Retention of LDL cholesterol in susceptible segments of the arteries is a key event in atherosclerotic injury (11). This accumulation of lipids triggers a reactive inflammatory process with the release of toxic substances and the ingrowth of smooth muscle cells. The muscle cells form a fibrous cap facing the vascular lumen, covering the underlying lipids and inflammatory cells in the atherosclerotic lesion (plaque). The atherosclerotic plaque thus consists of a fibrous cap of varying thickness and an underlying core containing varying amounts of lipids, inflammatory cells and fibrous connective tissue. As will be discussed later, the morphological characteristics of the plaque are critical determinants of subsequent disease progression.

As the plaque increases in size, it can lead to local stenosis of the artery. This results in reduced blood flow and oxygen supply to areas distal to the plaque. Ischaemic pain occurs when oxygen demand exceeds supply, for example during physical exertion or increased sympathetic nervous system activity in psychological stress.

Benign and malignant atherosclerotic plaques

Angina pectoris is in itself a benign condition, and the prognosis is favourable provided thrombotic complications can be avoided. It is thrombosis in association with an atherosclerotic plaque that transforms an otherwise benign condition into a life-threatening one, and which underlies the acute coronary syndromes, namely unstable angina pectoris, acute myocardial infarction and sudden death. Over the past decade, significant advances have been made in understanding the mechanisms that determine why some plaques remain resistant to thrombosis and relatively 'innocent' while others, after many years of slow growth, become thrombotic and life-threatening (10). Plaque vulnerability – its propensity to predispose to thrombosis – has been shown to be more important than plaque size and degree of stenosis.

Plaques with a soft, lipid-rich atheromatous core are particularly hazardous, as their instability predisposes to fibrous cap rupture. This exposes the plaque's lipid-rich necrotic core to circulating coagulation factors and platelets, with tissue factor acting as the principal thrombogenic stimulus. Platelets adhere to the exposed tissue, become activated, and a thrombus forms that can occlude the blood vessel. Approximately 75 % of all acute coronary syndromes (including acute myocardial infarction) are due to plaque rupture. The remaining cases are attributable to superficial erosion of the cap, in which coagulation factors are activated by collagen beneath the endothelial layer.

The factors influencing plaque vulnerability are not fully elucidated. The size of the lipid core is known to be important (10). Post-mortem studies have shown that ruptured plaques tend to have a relatively larger lipid core than non-ruptured plaques, in which fibrous connective tissue and smooth muscle cells constitute a greater proportion of the core. Vulnerable plaques have thinner caps and contain more inflammatory cells than stable plaques. Inflammation can weaken the cap, rendering it more susceptible to rupture. In addition to intrinsic plaque characteristics, 'external factors' also impact on the likelihood of rupture. These 'rupture triggers' can include blood pressure, pulse pressure, myocardial contraction and vasospasm. Increased activity of the sympathetic nervous system, with sudden rises in blood pressure, heart rate and myocardial contractility, is likely to trigger plaque rupture.

A useful simplification in this context is the distinction between 'benign' and 'malignant' forms of atherosclerotic plaque. Benign plaques are stable and have a low tendency to rupture, partly because they contain a relatively small proportion of lipids in the core. These plaques can cause angina pectoris, but not myocardial infarction. Malignant plaques are unstable, prone to rupture and characterised morphologically by a large, lipid-rich core, and can lead to myocardial infarction or sudden death.

Gender differences in the morphology of atherosclerotic plaque

Post-mortem studies have shown that the prevalence of atherosclerosis in the coronary arteries is higher in men than in women. In a large US study of people aged 15–64 years who died in traffic accidents or as a result of other trauma, the prevalence of atherosclerosis was found to be twice as high in men as in women (12). Unfortunately, the study did not include older age groups, and potential sex-based morphological differences in atherosclerosis were not assessed.

Over the past 10–15 years, high-resolution ultrasound technology has been developed that makes it possible to detect and classify atherosclerotic plaques in the carotid artery in vivo (13–16). The method is rapid, safe and relatively simple, and can therefore be used in large population studies. This has provided unique opportunities to study the prevalence of atherosclerosis as well as factors impacting on the risk of its development. A particular feature of the method is that it allows morphological classification of plaques (13). In ultrasound imaging, high-frequency sound waves are transmitted into the tissue. Depending on tissue density, the waves are reflected back and detected by a receiver, which constructs an image of the tissue. High-density tissue (e.g. fibrous connective tissue) produces strong reflection of the sound waves, while softer tissue (e.g. lipid deposits) produces weaker reflection. Validation studies have shown that echolucent (soft) plaques contain cores with a high lipid content, while echogenic (hard) plaques predominantly have cores composed of fibrous tissue.

Unfortunately, no non-invasive methods are currently available for the in vivo diagnosis of coronary atherosclerosis. However, plaques in the carotid artery are morphologically similar to those in the coronary arteries, and the mechanism of atherosclerotic development is likely the same (10). Several studies have shown that atherosclerosis in the carotid artery also tends to be accompanied by atherosclerosis in

the coronary and other peripheral arteries, which is not surprising given that atherosclerosis is a systemic disease. Thus, studies of the carotid artery can probably be used as a model for the coronary arteries.

In the Tromsø Health Survey conducted in 1994–95, more than 6000 men and women aged over 25 years were examined using carotid ultrasound (13). The prevalence of atherosclerotic plaques increased with age: from 3 % in the 25–34 years age group to over 70 % among the 70+ group. Up to the age of 70, prevalence was higher among men than women, but in those over 70 years the proportion of men with atherosclerosis was slightly lower than that of women. This was an unexpected finding. Even more surprisingly, the prevalence of echolucent (i.e. lipid-rich) plaques was higher in men than in women (14), and men were 40–50 % more likely to have a soft plaque. Perhaps most strikingly, this gender difference in plaque morphology did not change with age, and was present even in the oldest age groups (14).

Findings from two studies of patient populations support the results from Tromsø. In a study published by the European Carotid Plaque Study Group, histological examination was performed on atherosclerotic plaques removed during surgery for carotid artery stenosis (17). In men, 27 % of plaque content consisted of soft, lipid-rich material, while the corresponding figure in women was 19 %. This difference was statistically significant. The same trend was observed in a separate study conducted in Italy. The findings from the population-based Tromsø study are particularly important because they are derived from a representative sample of the general population as opposed to selected patient groups.

The morphology hypothesis

If a similar gender difference in plaque morphology is also present in the coronary arteries, this could explain the gender differences in the incidence of coronary heart disease. If men, to a greater extent than women, develop lipid-rich, unstable plaques prone to rupture in the coronary arteries, this would account for the higher incidence of myocardial infarction in men. Conversely, if the overall prevalence of coronary atherosclerosis (the sum of stable and unstable plaques) is approximately the same in older men and women, as was observed in the carotid artery, this would explain why the incidence of angina pectoris is similar in older women and men. Both types of plaque can cause stenosis and reduce blood flow in the coronary arteries.

The 'morphology hypothesis', as outlined above, therefore proposes that men have a more 'malignant' form of atherosclerosis than women. If correct, this implies that some individuals (more men than women) are predisposed to developing lipid-rich plaques in the arteries. A limitation of the hypothesis is that it is based on findings from the carotid arteries. However, there is strong evidence of morphological similarities between atherosclerosis in the carotid and coronary arteries (16, 18). The literature in this area is nevertheless limited and further research is needed.

One further issue remains in our explanatory model: why would women be less predisposed than men to developing lipid-rich atherosclerotic plaques?

Gender differences in coronary risk factors

There is no evidence that the established risk factors for myocardial infarction (age, LDL cholesterol, HDL cholesterol, blood pressure and smoking) act substantially differently in men and women (9, 19). The relative risk, or the change in risk per unit increase in risk factor level, is quite similar in men and women, with the exception of smoking and diabetes, which appear to be stronger risk factors in women than in men. The levels of these risk factors do, however, differ somewhat between the sexes. Up to the age of 60–70 years, women have slightly lower levels of LDL cholesterol and blood pressure than men, while the reverse is seen in older age groups.

HDL cholesterol, which is involved in the transport of cholesterol from peripheral vessels to the liver and is protective against myocardial infarction, is similar in both sexes until puberty (20). At puberty, levels decline in boys and remain lower in men than in women throughout life. HDL cholesterol is in fact the only established risk factor for myocardial infarction in which women are consistently favoured over men throughout the life course (21). The low HDL levels in men may be due to the sex hormone testosterone. Experimental studies have shown that physiological concentrations of testosterone reduce HDL cholesterol levels in men to an extent corresponding to the difference in HDL levels between men and women (22). This may explain the reduction in HDL cholesterol observed in boys during puberty (20).

The classical risk factors for myocardial infarction are also risk factors for atherosclerosis (15). High levels of LDL cholesterol, elevated systolic blood pressure and smoking increase the risk of atherosclerosis, while high levels of HDL cholesterol are protective. However, less is known about the mechanisms by which these risk factors act at the level of the atherosclerotic plaque.

A recently published study from the Tromsø population surveys has, for the first time, demonstrated an association between high HDL cholesterol levels and a lower prevalence of echolucent, lipid-rich atherosclerotic plaques (15). This finding from a large-scale epidemiological study confirms results from experimental animal models, which showed that increasing HDL levels leads to more fibrotic and stable atherosclerotic plaques with reduced lipid content (23). HDL appears to be able to 'deplete' plaques of lipids, probably because HDL particles contain the enzymes LCAT (lecithin–cholesterol acyltransferase) and CETP (cholesteryl ester transfer protein), both of which are involved in reverse cholesterol transport. In addition, HDL particles contain proteins that inhibit inflammatory responses. These effects make the plaque more stable and less vulnerable to rupture.

Conclusion

The gender difference in the risk of coronary heart disease is striking because it is observed in all countries and cultures. This suggests that sex hormones are involved. There is no evidence from epidemiological observational studies or controlled clinical trials that oestrogen protects women against coronary heart disease. The following hypothesis is proposed in this paper: men have a higher risk of coronary death and

myocardial infarction than women, owing to a greater propensity to develop lipid-rich, unstable and thrombogenic atherosclerotic plaques. This may be attributable to gender differences in HDL levels, which are in turn impacted by testosterone. The hypothesis is consistent with epidemiological observations and experimental findings, and accords with current understanding of the pathophysiological mechanisms underlying atherosclerosis and coronary heart disease. Nevertheless, further research is needed before the hypothesis can be regarded as confirmed.

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