Factors that underlie the gender differences in cardiovascular diseases

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Abstract

For both men and women cardiovascular diseases are the number one cause of death in the world. More and more research shows that there are gender differences in the prevalence and outcome of cardiovascular diseases. However, why these gender differences in cardiovascular diseases exist is not fully understood. Therefore the aim of this essay is to find out which factors underlie the gender differences in cardiovascular diseases.

Women develop cardiovascular diseases 7 to 10 years later than men. Also the type of cardiovascular diseases that men and women develop is different. As a first manifestation, women show most times cerebrovascular diseases, where men show most times coronary heart disease. There are a lot of studies that suggest gender differences in symptom presentation when experiencing cardiovascular diseases. It appears that women have more frequently atypical symptoms, which is partly due to a different pain perception and symptom reports. However, studies do not agree on the details of these gender differences. Besides, there are also gender differences in the effect of the therapy of cardiovascular diseases, like lifestyle changes, the use of statins and hormone replacement therapy.

Several studies suggest gender differences in the risk factors of cardiovascular diseases, like the effect of smoking, obesity, the metabolic syndrome, psychological factors and in diseases like diabetes mellitus. However, the studies disagree on the details. The main gender difference that has been found is the difference in lipid profile. Premenopausal women show lower LDL cholesterol levels and higher HDL cholesterol levels than men. After menopause women develop a higher LDL cholesterol level than men due to a decrease in oestrogen levels. Women show therefore more cardiovascular diseases at this age. Oestrogen has a protective effect when it comes to cardiovascular diseases.

In conclusion, hormone differences play an important role in the gender differences in cardiovascular diseases, mainly because of the impact on the lipid profile. However, it cannot declare all gender differences. Also gender differences in the prevalence of the risk factors play a role. Studies still disagree on the details. Probably a combination of several factors is responsible for the gender differences in cardiovascular diseases. However, more research and clinical trials with women are needed to find out all the factors.

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Introduction

Cardiovascular diseases are the number one cause of death in the world (1). According to the World Health Organization (WHO) 31 % of the deceased people in 2012 is due to cardiovascular diseases, which means about 17,5 million people died from cardiovascular diseases. Especially in countries with a low and middle income, people die of cardiovascular diseases. As the name suggests, cardiovascular disease is a collective name for diseases of the heart and blood vessels. Diseases that are included are coronary heart disease, myocardial infarct, heart failure, cerebrovascular diseases, peripheral arterial diseases, rheumatic heart disease, congenital heart diseases, thrombosis and embolism. The prevalence of these different cardiovascular diseases differs between men and women (2); the reason for this is not completely understood.

There are several risk factors for the development of cardiovascular diseases. Some of these risk factors are obesity, physical inactivity, smoking and excessive alcohol consumption (1, 3-4). The diet also plays an important part in the development of cardiovascular diseases. A high amount of dietary fat, cholesterol and salt will increase the risk of developing cardiovascular diseases. A high amount of fat in the diet leads to high plasma triglyceride levels, which is also associated with a higher risk of developing cardiovascular diseases (1, 5-7). To prevent cardiovascular diseases several of these risk factors can be reduced by adapting people's lifestyle. Besides that, the existence of diabetes mellitus and glucose intolerance, migraine, hypertension and hyperlipidaemia are risk factors for the development of cardiovascular diseases (1, 8-9). Also, the socio-economic status of humans plays a role, especially education (10-11). As mentioned before, in countries with a low and middle income more people die of cardiovascular diseases compared to countries with a high income (1). In countries with a high income more prevention is taken and health care is more accessible. It is also shown that a low birth weight is associated with a higher risk for developing cardiovascular diseases (12). However, some of these risk factors differ in men and woman (13).

The risk factors mentioned above cannot completely explain the prevalence and outcome of cardiovascular diseases in men and women. As described above, several studies showed that there are differences between men and women in the prevalence and outcome of cardiovascular diseases (13). According to the American Heart Association, in 2009 more women have died from cardiovascular diseases compared to men (14). However, in 2010 more men were diagnosed and treated for cardiovascular diseases. Besides these statistics, men and women show different symptoms when experiencing cardiovascular diseases and they develop cardiovascular diseases at a different age (2). There is also a difference found in the type of cardiovascular disease that men and women develop, as mentioned before. Men and woman also show a different reaction to therapies for cardiovascular diseases (15-16). Later in this essay I will discuss these differences.

The existence of the gender difference in the prevalence and outcome of cardiovascular diseases suggest that there are more factors involved in the development in cardiovascular diseases. These have to be factors that can also declare these gender differences. Recently more and more research has been done with regard to the gender differences in cardiovascular diseases. However, it is not completely clear which factors cause these gender differences. In this essay I will discuss the gender differences in cardiovascular diseases and I will figure out which factors underlie these differences between men and women. Therefore the main question in this essay is 'which factors underlie the gender differences in cardiovascular diseases?'. To answer this question, first the gender differences in cardiovascular diseases will be explained. Then I will discuss which factors are associated with these gender differences. In the end I will explain what impact these gender differences have on the therapy for cardiovascular diseases.

Chapter 1
Gender differences in cardiovascular diseases

To determine which factors underlie the gender differences in cardiovascular disease, I have to determine what the gender differences are first. Cardiovascular diseases are sexual dimorphic diseases, because after correction for known risk factors, still a gender difference will be found in presentation and outcome (17). In this chapter I will describe the gender differences in presentation and outcome of cardiovascular diseases.

Age and type of cardiovascular disease

There has been found a difference in the age at which cardiovascular diseases develop. The clinical symptoms of cardiovascular diseases develop 7 to 10 years later in women than in men (18-19). Women with an advanced age suffer more often from comorbidities, like diabetes mellitus, hypertension and post-menopausal hormone regulation. Therefore they have a high risk of developing cardiovascular diseases. This will also be discussed in the next chapter of this essay.

The prevalence of ischemic heart disease is decreasing in men, however not in women (18). The amount of women that are dying from cardiovascular diseases is increasing (19). This has to do with the differences in the underlying mechanisms (18). Women have more often non-obstructive epicardial artery disease, non-atherosclerotic spontaneous coronary artery dissection, stress cardiomyopathy, plaque erosion, microvascular dysfunction and heavier risk burden, even after adjusting for age. The outcome of acute and chronic cardiovascular diseases are worse in women than in men, in relation to older age and comorbidities.

As mentioned before, men and women develop cardiovascular diseases at a different age. However, at age 55 men and women have a similar lifetime risk of developing cardiovascular diseases (20). Though there are gender differences in the first manifestation of cardiovascular diseases. The first manifestation in men is very often a coronary heart disease, while women suffer most times a cerebrovascular disease (stroke, transient ischaemic attack or carotid revascularisation) or heart failure. However, these manifestations in women develop most times at an older age (figure 1).
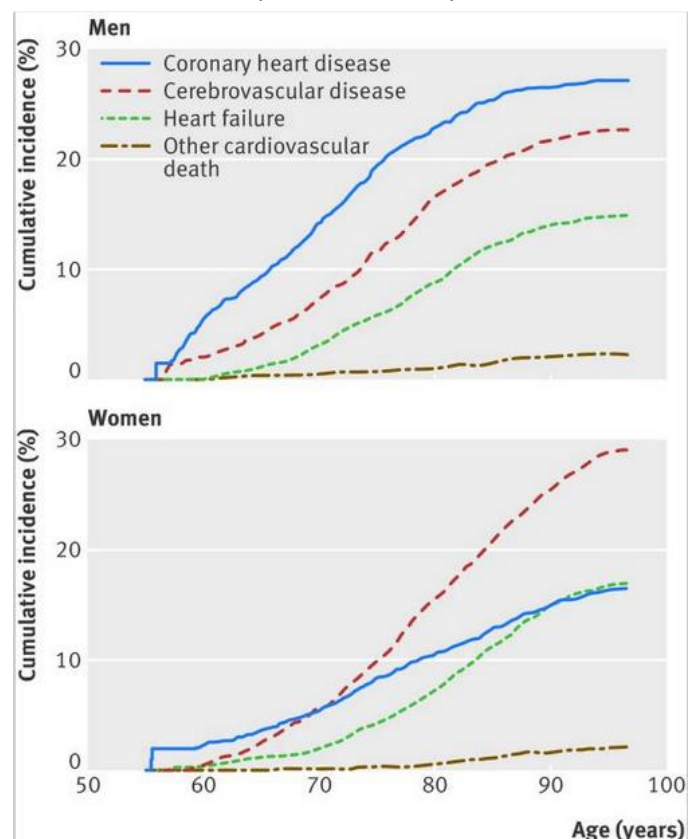

Figure 1 : Incidence of coronary heart disease, cerebrovascular disease, heart failure and other cardiovascular death shown for men and women by age (20).

Symptoms

Several studies show that there are gender differences in symptoms presented by men and women. There are also gender differences found in the presentation of angina pectoris. Symptoms of angina pectoris are more common in men and are reported at a lower age. Men report more often symptoms of typical angina pectoris, like retrosternal pain, pain related to effort and emotion and a reduction of the symptoms by rest or nitro-glycerine treatment. These gender differences are probably due to a difference in pain perception and reporting the symptoms, as described before (21, 22). Angina pectoris is the most common first presentation of cardiovascular disease in woman (23-25). Women are, compared to men, older, have more often hypertension and are less frequently smokers, when they experience this first presentation. Women show at a younger age (<55 years) especially atypical symptoms. When women get older, the symptoms of angina pectoris become more typical and similar to those in men (21). However, women show more functional impairment and have more unstable symptoms compared to men (26). So, stable angina pectoris affects fewer and older women than men. However, it is the most common initial presentation of ischemic heart disease among women, and symptoms become more typical with an advanced age.

Women show more often atypical symptoms of ischemic heart disease (18). However, it is also shown that there are gender differences in pain perception and reporting these symptoms (21, 27). Automatically there will be gender differences in presentation of symptoms in cardiovascular diseases. Chest pain after the onset of an ischaemic infarct is very often sooner experienced by women than men and the described pain has a higher intensity according to women. However, the type of pain that women report is less specific, with the consequence of lower rates of diagnostic testing (28-29). The pain is not described as the typical crushing central chest pain, which means that women are more likely to be misdiagnosed (19, 30). Although, not all studies confirm these gender differences in chest pain (31). Though, men that undergo an acute myocardial infarct show less often neck pain, back pain, jaw pain and nausea, compared to women. However, men are more likely to have complaints of diaphoresis. As also will be discussed in chapter 3, there are also gender differences found in diagnostics and management. Because there are gender differences in symptoms of cardiovascular diseases, there are also gender differences in diagnostics. Naturally women have a higher heart rate at rest and show therefore a longer QT-interval on an ECG, compared to men (21, 32). In younger women, endogenous oestrogen can cause ECG changes mimicking ischemia, which can also lead to misdiagnosis (22).

Chapter 2
Factors that underlie the gender differences in cardiovascular diseases

In the introduction and chapter 1 the risk factors of cardiovascular diseases and the gender differences have been discussed. In this chapter I will explain which factors underlie these gender differences in cardiovascular diseases. I will discuss the gender differences in the risk factors of cardiovascular diseases, the role of hormones and the molecular and cellular gender differences. In chapter 1 I have already mentioned the gender differences in pain perception and reporting the symptoms of cardiovascular disease.

The risk factors

The risk factors of cardiovascular diseases have already been mentioned in the introduction. There are several differences found between men and women when it comes to these risk factors. It is found that smoking is a significant higher risk factor for women to develop cardiovascular diseases, especially in younger women (13, 33-34). This gender difference might be due to the fact that women have a greater potential to absorb toxic chemicals from the same amount of cigarettes (35). There are also risk factors that have a much higher prevalence in women than men (36-37). For example migraine is three times more common in women than man and it is associated with a higher risk of developing cerebrovascular diseases, like a stroke. It is also shown that women more often experience lifestyle and psychological factors, like physical inactivity, depression and stress, that are associated with a higher risk of developing cardiovascular diseases (18). Other important risk factors that show gender differences are the presence of diabetes mellitus, obesity and the metabolic syndrome. These major risk factors will be discussed in more detail in the next paragraphs. An overview of the risk factors and the gender differences in cardiovascular diseases is shown in figure 3 later in this chapter.

Also, in harmful diseases like diabetes mellitus gender differences have been found. The prevalence of diabetes mellitus is increasing (38-39). As described in the introduction, diabetes mellitus is a risk factor for cardiovascular diseases in men and women. However, more men than women suffer from diabetes mellitus, which is partially an explanation for the fact that women are less often diagnosed with cardiovascular diseases (40-41). Diabetes mellitus is very often diagnosed at an advanced state (42-43). At this stage vascular complications and metabolic alterations have very often already occurred. However, the effect of the presence of diabetes mellitus on developing a stroke is greater in women than in men (13). In addition women with diabetes mellitus have more often vascular complications and metabolic alterations, which can be due to the fact that women with diabetes mellitus are more often undiagnosed and untreated (13). Though this is not confirmed by other studies (44). Besides that, the effect of type 2 diabetes mellitus on the development of cardiovascular disease is greater, compared to men (45). This is partly explained by a higher blood pressure and atherogenic dyslipidaemia in women with type 2 diabetes mellitus. Taken this all together, there are several gender differences when it comes to the risk factor diabetes mellitus. However, some studies suggest that men have more often diabetes mellitus and are therefore more prone to develop cardiovascular diseases and other studies suggest that women are more susceptible to develop cardiovascular diseases, because of the reasons described above.

In the introduction obesity was mentioned as a risk factor for cardiovascular diseases. This is a risk factor that is especially common in high-income countries. In high-income countries the BMI (body mass index) is higher in men than in women; in low-income countries the women have a

higher BMI (46). The risk for developing a stroke associated with BMI is higher in men than in women (47-48). However, the effect of the BMI on developing cardiovascular diseases in general is similar in men and women. Men have a higher risk for developing cardiovascular diseases, because they have in general, especially in high-income countries, a higher BMI. There can also be looked at body fat distribution, besides the BMI. Although, there is a gender dimorphism in body fat distribution, there is no direct association found between body fat distribution and the risk of developing cardiovascular diseases (48). However, women that have more often central obesity are more likely to develop type 2 diabetes mellitus, which is also a risk factor for developing cardiovascular diseases (44).

Several of the risk factors of cardiovascular diseases are present in the metabolic syndrome. The metabolic syndrome consists of the coexistence of the lipid triad (elevated serum triglyceride levels, small LDL particles and low HDL cholesterol), hypertension, insulin resistance, glucose intolerance and a pro-coagualate state (49). There are gender differences known in the metabolic syndrome, which can contribute to the gender differences in cardiovascular diseases (44).The prevalence of the metabolic syndrome is higher in men than in women. However, the prevalence in women is increasing a lot. As I will discuss later in this chapter, lipid profiles differ between men and women. As described above, obesity and diabetes mellitus are important risk factors for developing cardiovascular diseases and there are gender differences found when it comes to these risk factors.

The lipid profile and hormones

As mentioned before, an unfavourable lipid profile plays a role in the development of cardiovascular diseases. Studies have also found gender differences when it comes to the lipid profile. Hormones play an important role in these gender differences. In this paragraph the gender differences in lipid profile and the effects of hormones will be discussed (see figure 3 for an overview).

Pre-menopause

It is shown that pre-menopausal women have a more favourable lipid profile, compared to men (50-51). Studies suggest that the hormone oestrogen in the blood is interfering with the LDL (low density lipoprotein) uptake in the arterial wall (52). Therefore the same LDL cholesterol level is less atherogenic in women than it is in men. The high LDL cholesterol levels are correlated with a higher risk of developing cardiovascular diseases (53). When HDL (high density lipoprotein) cholesterol levels increase the risk of developing cardiovascular diseases decreases. The effect of high LDL and high HDL cholesterol levels is similar in men and women. However, the total HDL cholesterol levels are higher in women and leads therefore to a smaller risk of developing cardiovascular diseases (54). HDL cholesterol levels in men undergo a decrease during puberty. This is not seen in women. It is tempting to speculate that these changes in men are due to androgens and that rising oestrogen levels in women at this age prevent the decrease in HDL cholesterol levels (55). Therefore women have their whole live a higher HDL cholesterol level than men (figure 2).

Also during the menstrual cycle of women oestrogen levels have a great influence on the lipid profile (56). In the first part of the cycle, when oestrogen levels are increasing, LDL cholesterol levels decrease and remain low, also during the second half of the cycle, in which progesterone is dominated. The changing progesterone levels during the cycle have no effect on the lipid profile (57). During the menstrual cycle, HDL cholesterol levels remain the same. However, it is not known why the increasing oestrogen levels in the first half of the cycle do not lead to an increase in HDL cholesterol level.

As well during pregnancy the lipid profile changes, because of the hormonal changes in which both oestrogen and progesterone levels increase enormously (58). These hormonal changes lead to an increase in LDL cholesterol levels and these levels stay high until a few weeks after the delivery. During pregnancy, first the HDL cholesterol levels increase until the 24th week and then the HDL cholesterol levels decrease again. Not only LDL and HDL cholesterol levels change during pregnancy, but also the triglyceride levels change. During pregnancy the triglyceride levels increase. However,

very soon after delivery the triglyceride levels go back to normal (59). So, during pregnancy there are different changes in lipid profile. These changes suggest that multiple pregnancies lead to a higher risk of developing cardiovascular diseases later in life. Although, studies have failed to demonstrate that multiparity leads to a higher risk of developing cardiovascular diseases (60).

Also disorders during pregnancy, like gestational hypertension, pre-eclampsia and gestational diabetes mellitus, increase the risk of developing cardiovascular diseases (61-64). These pregnancy outcomes give information about the cardiovascular health of the mother and will possibly lead to a higher risk of developing cardiovascular disease. Also, women that have experienced gestational diabetes mellitus during pregnancy, have a higher risk to develop diabetes mellitus type 2 later in life, which is also an extra risk factor for developing cardiovascular diseases. Besides, foetal and placental complications during pregnancy give also rise to the risk of developing cardiovascular diseases for the mother (65). The mechanism how these factor increase the risk of developing cardiovascular diseases is still unclear. Studies suggest that women that experience these disorders during pregnancy had already a higher risk of developing cardiovascular diseases before the pregnancy. However, other studies suggest that women obtain the higher risk of developing cardiovascular diseases after experiencing these disorders during pregnancy. It is also shown that only parity itself increases the risk of developing cardiovascular diseases (66).

In women the effect of oral contraceptives on the lipid profile and the risk for cardiovascular diseases has been examined. As mentioned before, oestrogens have a favourable effect on the lipid profile by decreasing LDL cholesterol levels and ilow ncreasing HDL cholesterol levels. The decrease in LDL cholesterol levels is affected by enhancing the LDL-receptor activity (67). The lowering of LDL cholesterol levels lead to an inhibition of hepatic lipase and therefore an increase in HDL cholesterol (68). The oral contraceptives, especially the older ones, may also have a negative effect on the lipid profile by increasing the triglyceride levels (69). However, the use of oral contraceptives is temporary and when the use of oral contraceptives stops, also the negative effect on the lipid profile disappears. Besides, the protective effects of oestrogens lead to the fact that the use of oral contraceptives has not an impact on the risk of developing cardiovascular diseases.

Like described above, hormones and hormonal changes have an impact on the lipid profile and therefore on the risk of developing cardiovascular disease. However, the risk of developing cardiovascular disease is also increased by endocrine disorders in younger women , like for example polycystic ovary syndrome and early menopause (13). Polycystic ovarian syndrome is characterized by an excessive production of androgens, which leads to ovarian dysfunction, menstrual disorders, fertility problems and insulin resistance (70-71). The polycystic ovarian syndrome is also associated with the metabolic syndrome (72), which has already been mentioned as a risk factor for developing cardiovascular diseases.

Post-menopause

After menopause, the LDL cholesterol levels rise and the LDL cholesterol levels become higher than that of men (figure 2) (50-51). This suggests that hormones play an important role. In postmenopausal women the LDL cholesterol levels increase significantly and levels become unfavourable (55). The LDL cholesterol levels are in postmenopausal women higher than the LDL cholesterol levels in men of the same age. However, HDL cholesterol levels do not change significantly in postmenopausal women. This demonstrates that women have a more unfavourable lipid profile when they pass menopause. However, the decrease in oestrogen level after menopause has not only a negative effect on the lipid profile (73). The lower oestrogen levels have also an effect on the fat distribution, platelet function and it may worsen pre-existing diabetes mellitus and hypertension, which will all lead to a higher risk for developing cardiovascular diseases.

As mentioned in the introduction, high plasma triglyceride levels lead to an increased risk of developing cardiovascular diseases. Although, the exact role of triglycerides on the development of cardiovascular diseases is not fully understood. It seems like they are not an independent risk factor for cardiovascular diseases (74). However, again after menopause these factors change. In postmenopausal women the triglyceride level becomes an independent predictor for cardiovascular

diseases (75). Though, triglycerides do not accumulate in atherosclerotic plaques. This suggests that they are not a proximate cause of atherogenesis. But as mentioned before, triglycerides in postmenopausal women play an more important role. In postmenopausal women, triglycerides may be markers for the presence of other lipoprotein, like small dense LDL particles, that are atherogenic (76).
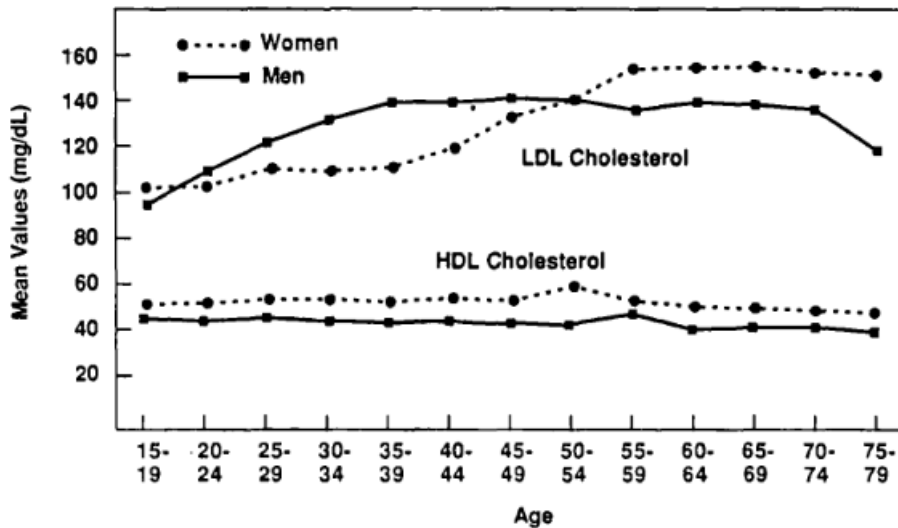

Figure 2: LDL and HDL cholesterol levels in men and women, shown by age (55).

Molecular and cellular gender differences

As described in the previous paragraph, women develop cardiovascular diseases at an advanced age due to the hormonal changes during menopause. In this paragraph I will explain what the molecular and cellular mechanism is behind this. Also, I will discuss what other molecular and cellular gender differences have been found when it comes to cardiovascular diseases.

The steroid hormones bind to nuclear receptors that are present in vascular endothelial cells, vascular smooth muscle cells and cardiomyocytes (77). This suggests already that steroid hormones play a role in the development of cardiovascular diseases. At first, there is coregulation of steroid hormone receptors with certain protein (78-79). It is known that there are differences in amount of expression of these coregulatory proteins in vascular and myocardial cells. Individual differences in the expression of these protein and receptors are associated with differences in the risk for developing cardiovascular diseases.

Oestrogen promotes re-endothelialisation and inhibits smoot muscle cell proliferation, matrix deposition and atherosclerotic plaque formation, when a blood vessel is injured (80-83). Oestrogen also can lead to the production of prostacyclin, which is an atheroprotective molecule. These types of effects are not found for hormones like progesterone or testosterone.

Oestrogen has also an effect on the blood pressure by increasing the NO (nitric oxide) production and inducing NOS genes, which will lead to a lower blood pressure (84-85) (figure 3). This suggests that pre-menopausal women have a lower blood pressure and show therefore less cardiovascular diseases at this age. However, administration of oestrogen for a short term has little effect on the blood pressure in men. Though, administration of oestrogen for a long term will show a significant vasodilatation and lowering of blood pressure in men (86). The oestrogen receptor ERβ is necessary for vasodilatation and regulation the blood pressure in both women and men. However, men have less ERβ receptors, which means that they have a higher blood pressure compared to women (87). Also men have a low amount of oestrogen. By aromatase testosterone can be converted into oestrogen, which has a positive effect on the vasodilatation of the blood vessels (88-89). Men without the ERβ receptors have a decreased vascular function and develop sooner

cardiovascular diseases (90). Besides oestrogen, also progesterone can decrease the blood pressure (91). Though, synthetic progestins may raise the blood pressure.

The heart function differs between women and men. Women show a greater cardiac contractility and their myocardial mass is better preserved with ageing, compared to men (92-94). These differences may result from a difference in cardiac expression of glycolytic and mitochondrial metabolic enzymes or the effects of oestrogen on the cardiomyocytes. It is also shown that after a myocardial infarct, oestrogen shows a positive effect and testosterone worsens the heart function (95).
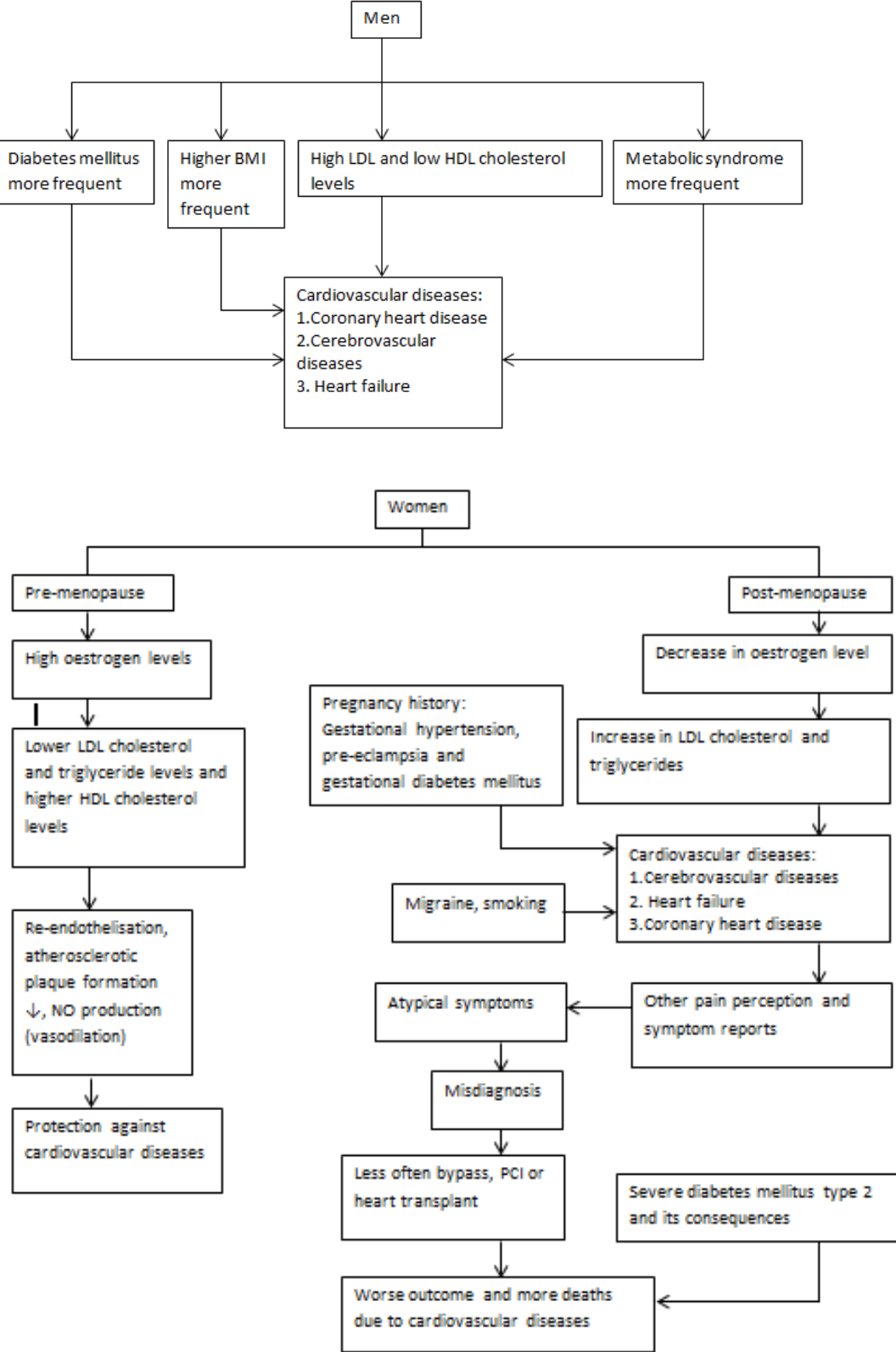

Figure 3: Factors that underlie the development of cardiovascular diseases shown for both men and women.

Chapter 3
Gender differences in management and therapy of cardiovascular diseases

In the previous chapters the gender differences in cardiovascular diseases and the factors that underlie these differences have been discussed. Because of the gender differences in cardiovascular diseases, new insights in management and therapy are required. The management and therapy of cardiovascular disease has to be adapted to the gender of the patient. In this chapter I will discuss the gender differences in management and therapy of cardiovascular diseases.

Gender differences in management

According to the American Heart Association, in 2009 men represent 49% of deaths from cardiovascular disease (14, 18). Women represent 51% of deaths from cardiovascular disease. However, 3,0 million men were diagnosed with cardiovascular disease in 2010, compared to 2,8 million women. Also in 2010, 74,9% of the patients who underwent bypass, 67,1% of the PCI (Percutaneous coronary intervention) patients and 68,7% of heart transplant patients, were men. This compared to respectively 25,1%, 32,9% and 31,3% of women. This is probably due to more misdiagnoses in women than in men. It is also known bypass is less effective in women than in men. This is due to the fact that women have smaller diameter vessels and show less revascularisation (16). Because of the more frequent misdiagnoses in women, women receive less diagnostic procedures and optimal treatment (19). For example women experience less often invasive imaging (18). This is also one of the reasons why women experience more often worse outcomes, including death, compared to men. It is still not fully known what the optimal treatment is for women with cardiovascular diseases. This is also due to the fact that women are underrepresented in clinical trials with cardiovascular diseases.
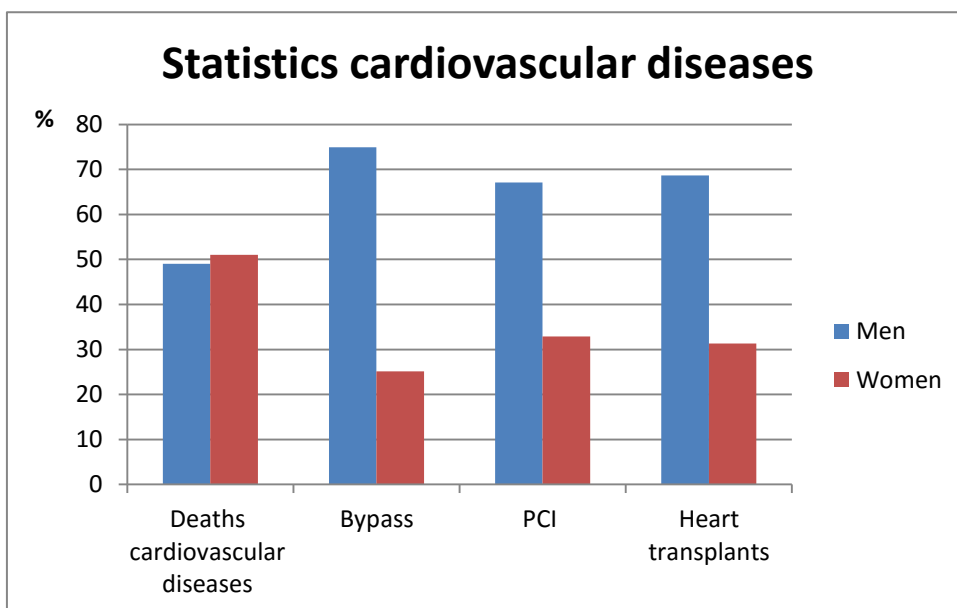

Figure 4: Statistics of cardiovascular disease shown for men and women. PCI=percutaneous coronary intervention (based on statistics of the American Heart Association) (14).

Gender differences in reaction to therapy

When women are diagnosed correctly, they do not always react very good to the therapy they were given. Men and women react already different to lifestyle changes (55). By changing the diet into a low fat and low cholesterol diet, a lowering in triglyceride levels and cholesterol levels (LDL and HDL) is experienced. Although premenopausal women show less lowering of triglyceride levels and LDL cholesterol levels, compared to men of the same age. Though HDL cholesterol levels decreased more in women than men. In postmenopausal women, the cholesterol lowering effects are greater. Weight loss also leads to a reduction in cholesterol levels. However, also weight loss appears to be less effective in women than men. The HDL levels were lowered in women, but increased in men with a similar weight loss. In addition, in premenopausal women exercise is less effective in lowering the LDL cholesterol levels and increasing the HDL cholesterol levels, compared to men. So, lifestyle changes like switching diet, weight loss and more exercise, are more effective in men than in women. The reason for this is not fully understood. Possibly, again the hormones play an important role in these gender differences. Oestrogen may act as a physiologic buffer to maintain lipoprotein levels when environmental changes occur.

Not only the effect of lifestyle changes are different in men and women, but also the effect of certain medication, like statins. Statins lower the cholesterol levels and inhibit therefore atherosclerosis (96). In both men and women the use of statins leads to an atheroma regression. However, the effect in women is greater than in men. The long term use of maximally intensive statin in women, especially rosuvastatin, results in a greater atheroma regression than in men. This difference in reaction to statins is especially seen when LDL cholesterol levels become below 70 mg/dl. However, it is not known if statins lower directly cholesterol levels or that cholesterol levels are lowered by other effects of statins (97). It seems that statins can also improve the endothelial function, the effects of antioxidants and it can increase the NO availability. Besides, statins can lead to an inhibition of inflammatory responses and to a stabilization of atherosclerotic plaques. All these effects can also lead to a lower risk of developing cardiovascular diseases.

As shown in the previous chapter, hormones play an important role in the gender differences of cardiovascular diseases. Therefore there are some indications that hormone replacement therapy (HRT) with oestrogen has a protective effect on the development of cardiovascular diseases in women (77, 98). However, other studies contradict this. So, further research has to be done to determine if hormone replacement is a suitable therapy for women. The hypothesis at the moment is that HRT can improve or reverse the endothelial dysfunction in blood vessels. It will lead to vasodilatation, less inflammation and it will inhibit lesion progression (figure 5). However, these positive effects are only present in the early stage of atherosclerosis. In later stages of atherosclerosis HRT will lead to less vasodilatation and
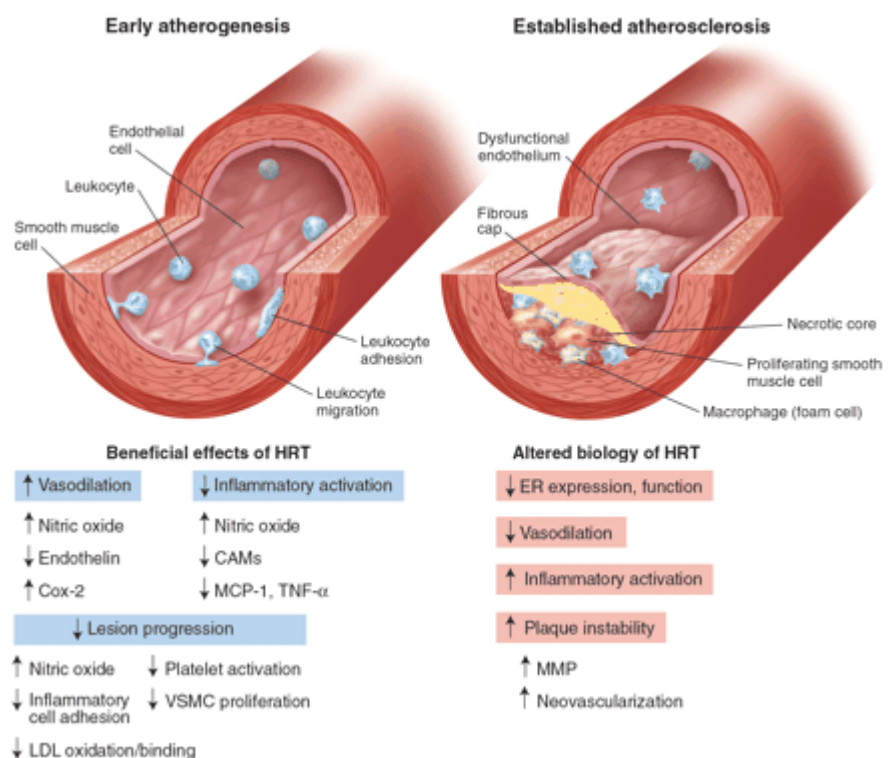

Figure 5: Effects of hormone replacement therapy (HRT) on an early stage of atherogenesis and a later stage of atherogenesis . LDL=low density lipoprotein; CAMs=cell adhesion molecules; MCP-1=monocyte chemoattractant protein 1; TNF-α=tumor necrosis factor–α; VSMC,=vascular smooth muscle cell; MMP=matrix metalloproteinase; COX-2=cyclooxygenase 2 (77).

endoplasmic reticulum function and to more inflammation and plaque instability (figure 5). As mentioned above, this is a hypothesis. So, further research has to be done to confirm this hypothesis and to find out if this is an appropriate therapy for cardiovascular disease in women.

Discussion

As described in the introduction there are a lot of risk factors for developing cardiovascular diseases. However, these risk factors cannot completely declare the prevalence and outcome of cardiovascular diseases in men and women. Men and women show differences in prevalence and outcome of cardiovascular diseases. Because of these gender differences also the management and the effect of the therapy appears to be different. In this essay I have discussed the gender differences in cardiovascular diseases. Also, I have explained which factors underlie these gender differences and what the impact is on the management and therapy of cardiovascular diseases.

The main differences in cardiovascular diseases that have been found are the age at which cardiovascular diseases emerge in men and women, the type of cardiovascular disease men and women develop and the symptoms that men and women show when experiencing cardiovascular diseases (18-20). Women appear to develop cardiovascular diseases 7 to 10 years later than men and they show most times cerebrovascular diseases as a first manifestation, where men show most often coronary heart disease. Also women show more atypical symptoms than men when experiencing an ischemic heart disease and angina pectoris. Probably a difference in pain perception and reporting the symptoms play a role. However, not all studies confirm these results or show the same results when it comes to the gender differences in experiencing symptoms in cardiovascular diseases. Though, it could be an explanation for why women are more often misdiagnosed and experience other management and therapies when it comes to cardiovascular diseases.

The gender differences in cardiovascular diseases can probably be declared by different factors, which is also shown in figure 3. Men have more frequently diabetes mellitus, a higher BMI, higher LDL cholesterol levels and lower HDL cholesterol levels and they have more often the metabolic syndrome compared to women (13, 18, 46, 49). These are all risk factors for developing cardiovascular diseases and men are in disadvantage at this point. However there are also risk factors that are more present in women, like smoking and migraine. Also the pregnancy history can be an indication of the risk of developing cardiovascular diseases later in life. In women there is a clear division in pre- and post-menopause when it comes to the risk of developing cardiovascular diseases (50-51, 55). It appears that premenopausal women show lower LDL cholesterol levels and higher HDL cholesterol levels compared to men. Though in postmenopausal women the LDL cholesterol levels become higher than that in men. These gender differences are due to hormones. The hormone oestrogen has a protective effect in the development of cardiovascular diseases by promoting re-endothelialisation and NO production for lowering the blood pressure and inhibiting smooth muscle cell proliferation, matrix deposition and atherosclerotic plaque formation. These statements can declare why premenopausal women show less cardiovascular diseases than men at the same age. A decrease in oestrogen after menopause leads to a more negative fat distribution and platelet function and it may worsen pre-existing hypertension and diabetes mellitus. Postmenopausal women experience therefore more severe diabetes mellitus than men. All these factors after menopause lead to a higher risk for developing cardiovascular diseases in postmenopausal women. So, oestrogen has a protective effect on the development of cardiovascular diseases. However, testosterone, which is most present in men, may worsen the heart function.

In the effect of therapy for cardiovascular diseases there has also been found a gender difference. Life style changes appear to be more successful in men than in women (55). However, the effect of cholesterol lowering medicine, like statins, is greater in women than in men (96). There are indications that hormone replacement therapy (HRT) is a new treatment for women to decrease the risk of developing cardiovascular diseases, in particular atherosclerosis (77, 96). However, some studies contradict this. Though, there is hypothesis that can explain these contradicting results. It is thought that HRT can improve endothelial function and vasodilatation and it can inhibit inflammation and lesion progression. Though these effects are only possible when there is an early stage of

atherosclerosis. At a later stage of atherosclerosis HRT has the opposite effect on the atherosclerotic plaque. However, this is only a hypothesis. So, more research is needed to confirm this hypothesis.

In conclusion, it is still not fully known which factors underlie the gender differences in cardiovascular disease, but it is probably a combination of several factors. Differences in the hormone composition between men and women and the impact on the lipid profile play an important role and can declare a major part of the gender differences in cardiovascular disease. Besides, gender differences in the prevalence of the risk factors also play a role. Though, in the future more research is needed to find out the details of these differences and what the differences in symptoms are and how these can be explained. Also more clinical trials with women are needed so cardiovascular diseases in women can be better diagnosed and it becomes more clear which therapy is most suitable for women with cardiovascular diseases.

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