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Is the impact of conventional risk factors the same in men and women? Plea for a more gender-specific approach

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ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death in women in developed countries. The traditional modifiable risk factors are able to explain the majority of CVD mortality. The aim of this review is to analyze gender-specific aspects of major conventional cardiovascular risk factors and to assess whether they have the same impact on CVD in women.

Cigarette smoking remains the single largest preventable cause of cardiovascular morbidity and premature death worldwide. Women smoke less than men; however, smoking seems to be more harmful in women, particularly in oral contraceptive users.

Obesity in the general population is more prevalent in women. Visceral adiposity is associated with insulin resistance and a higher risk of developing cardiovascular disease.

Life expectancy in female diabetic patients is shorter than in men with diabetes; women with diabetes are also at higher risk of developing cardiovascular events.

Changes of main lipid parameters in women are frequently associated with their hormonal status and/or hormonal treatment.

Hypertension is highly prevalent in post-menopausal women and carries a higher risk of developing left ventricular hypertrophy, which, together with a greater increase in vascular and myocardial stiffness, results in a higher incidence of heart failure with preserved ejection fraction and a higher risk of developing stroke. The risk of abdominal aortic rupture is substantially higher in women.

In conclusion, smoking, diabetes and hypertension seem to be more harmful in women. Therefore, the question is whether there should not be lower thresholds for initiating drug treatment in women with diabetes and hypertension.

1. Introduction

Cardiovascular disease (CVD) remains the leading cause of death in women in developed countries. The proportion of CVD-related deaths in Europe is greater in women than in men, contributing to their total mortality by 49% and only 40% in their male counterparts [1] (Fig. 1). The traditional potentially modifiable risk factors are able to explain about >90% of coronary heart disease (CHD) mortality worldwide [2]. However, there are important gender differences.

The aim of this paper is to review major conventional cardiovascular (CV) risk factors regarding their gender-specific epidemiology, pathophysiology and treatment and to analyze whether they have the same impact on CVD in women as in men.

2. Conventional risk factors

2.1. Cigarette smoking

Tobacco smoke from cigarettes is a major cause of CHD and remains the single largest preventable cause of CV morbidity and premature death worldwide.

A systematic review and meta-analysis of prospective cohort studies showed that smoking women have a 25% increased relative risk for CHD

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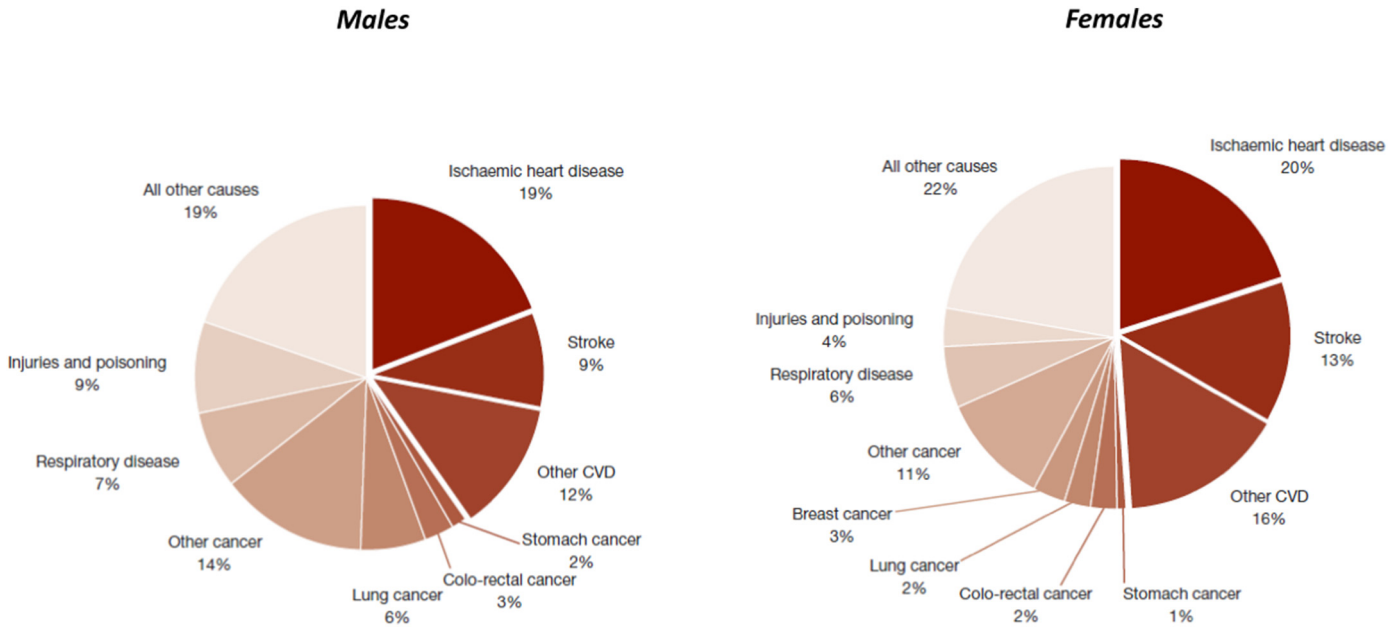

Fig. 1. Death rates in Europe 2014, males and females, latest available year (2014). Reprinted with permission from the European Heart Network.

compared with male smokers [3]. The "lost years of expected life" are particularly high for female light smokers (7.4 years vs. 6.0 years for male light smokers) [4].

Using the SCORE risk chart, smoking accounts for about 50% of total CV risk in both genders [5]. Quitting smoking is associated with the largest (about 50%) risk reduction within the next 24 months [6].

2.1.1. Epidemiology

Overall, the smoking epidemic typically starts by smoking among men, followed by female smoking reaching the highest prevalence years later, and remaining always at lower rates than in males [7].

Worldwide, men smoke almost five times as much as women; in high-income countries, women smoke at nearly the same rate as men while, in low- and middle-income countries, women smoke much less than men.

In Europe, the most recent available data reported higher prevalence of smoking [1] among adult men (27.1%) than among adult women (18.5%). Among men, the prevalence of smoking was highest in Eastern Europe and the former Soviet Union while being very low in women in the former Soviet Union, low in Eastern and Central Europe, and higher in Northern, Western and Southern European countries (UK and Denmark 17%, France 25%, Greece 26%).

2.1.2. Pathophysiology

Adverse effects of cigarette smoking on CVD and risk factors are listed in Table 1.

Smoking accelerates the development of both atherosclerosis and subsequent thrombosis, affects endothelial function, induces oxidative injury, chronic inflammation, hemodynamic stress, adverse effects on blood lipids, insulin resistance and diabetes, reduces oxygen delivery by red blood cells, and arrhythmogenesis [8].

Smoking seems to be more harmful in women because of enhanced nicotine metabolism and burning products effect, particularly in oral contraceptive users, affecting both platelet function and coagulation factors.

Cigarette smoking acutely increases systolic blood pressure (BP) and heart rate in both genders; however, the response is more enhanced in females [9].

2.1.3. Treatment

About 80–90% of smokers develop, in addition to psychobehavioral dependence, physical (drug) dependence. Evidence-based treatment consists of psycho-socio-behavioral intervention and pharmacotherapy (varenicline, bupropion, and/or nicotine replacement therapy) to suppress withdrawal symptoms [3].

Although female smokers tend to be more psychosocially than physically dependent, some studies show lower abstinence rates compared with males, usually heavier smokers. Smoking cessation initiated in the first half of the menstrual cycle may be more successful due to higher estrogen levels [10].

2.2. Obesity

Overweight is arbitrarily defined as a body mass index (BMI) ≥ 25 kg/m^2, with obesity defined as a BMI ≥ 30 kg/m^2. Although BMI represents the most powerful measure of obesity at the population level, it does not distinguish between lean and fat mass. Contrarily, increased waist circumference and waist-to-height ratio better evaluate central obesity.

The Framingham Heart Study found obesity to be associated with a higher relative risk of CHD in women (64% vs. 46% in men) [11].

Table 1
Cardiovascular disorders caused by cigarette smoking.

Vascular disease	**Arrhythmias**
Accelerated atherosclerosis	Sudden cardiac death
Acute myocardial infarction	Atrial fibrillation
Shorter exercise time to angina	Inappropriate ICD shocks
Coronary spasm	
Stroke	**Myocardial disease**
Aortic aneurysm	Increased risk and worsening of heart failure
Peripheral obstructive arterial disease	Hypertensive heart disease
Stent thrombosis after PCI	
Graft occlusion after CABG	**Effect on CV risk factors**
Erectile dysfunction	Type 2 diabetes
	Dyslipidemia
Macular degeneration	Hypertension

PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ICD, implantable cardioverter-defibrillator.
Adapted from Benowitz [8].

2.2.1. Epidemiology

According to the World Health Organization (WHO), the prevalence of obesity tripled between 1975 and 2016. In 2016, 13% of adults were obese (15% women, 11% men), with the highest age-adjusted obesity rates in America (29%), Europe (23%), and Eastern Mediterranean countries (21%) [12]. Across countries, obesity is consistently more prevalent among women, which is mainly attributed to pathophysiological differences. However, the prevalence gap between genders varies greatly by countries, which is explained by socio-economic factors, gender inequality and women's reproductive role [13].

In the general population, excess in white adipose tissue in obese individuals has been shown to increase the risk of CVD, metabolic syndrome, type 2 diabetes mellitus (T2DM), neurodegenerative diseases, and some cancers.

2.2.2. Pathophysiology

Men have more lean mass, visceral, and abdominal subcutaneous adipose tissue ("apple" phenotype), whereas pre-menopausal women have more fat mass and subcutaneous gluteal-femoral adipose tissue ("pear" phenotype). In obesity, adipocyte size increases in visceral and subcutaneous adipose tissue in both genders, while the number of adipocytes increases only in subcutaneous adipose tissue in women. Gender differences in adipose tissue distribution may underlie higher insulin resistance, enhanced gluconeogenesis and higher triglyceridemia in men, while greater subcutaneous gluteal-femoral fat may play a protective role in the development of metabolic syndrome and atherosclerosis in women.

Circulating and local sex hormones appear to be major modulators of adipose tissue distribution. Sex hormones serve as signals for adipocyte progenitor cells to proliferate and/or differentiate, and exhibit different actions in different fat depots, which, in the case of estrogen, are mediated by estrogen receptor subtype [14]. For instance, estrogen reduces food intake and central adiposity in both genders, whereas testosterone therapy decreases visceral fat and increases lipolysis in aging men while increasing visceral fat in obese post-menopausal women. Gender differences in adipose tissue distribution are attributed also to sex chromosomes. The potential mechanisms of action include increased expression of genes escaping X-chromosome inactivation.

Besides energy storage and thermoregulatory function, adipose tissue serves as an active endocrine organ secreting adipokines that regulate local and whole body metabolism. The levels of both major adipokines, i.e., leptin, a major regulator of energy homeostasis, and adiponectin, an insulin-sensitizing hormone, are higher in women [15].

Obese women, particularly those with visceral obesity, have a higher prevalence of subclinical cardiac disease (left atrial dilatation, abnormal left ventricular geometry) [16,17], carrying a higher risk for development of atrial fibrillation [18]. Epicardial adipose tissue and pericardial fat were recently found to be stronger predictors for atrial fibrillation than abdominal or overall adiposity [19].

2.2.3. Treatment

The main goals of obesity treatment are weight reduction with an emphasis on body composition, weight maintenance and prevention of weight gain. An optimal 5–15% weight loss over a period of 6 months (0.5–1 kg/week) is sufficient to achieve risk reduction in both genders [20].

Lifestyle interventions (diet and physical activity) should be recommended to all overweight and obese patients. Pharmacotherapy should be considered in overweight patients with a BMI ≥ 27 and co-morbidities and in all obese patients. Bariatric surgery should be considered in obese patients with a BMI ≥ 40, in obese patients with a BMI ≥ 35 and co-morbidities; and in obese patients with a BMI ≥ 30 and T2DM on an individual basis [20].

Guidelines on obesity management do not include any gender-specific recommendation. However, women exhibit higher susceptibility to obesity-related depression, emotional eating, and weight cycling, therefore psychological support appears to be important especially in women [21]. Also, interestingly, 80% of patients undergoing bariatric surgery are women, which is given mainly by psychological and socio-economic factors. Men tend to be older, have more co-morbidities, lower weight loss and higher rates of complications associated with bariatric surgery. Thus, earlier referral to surgery might help improve outcomes in men. Finally, women lose less weight in response to exercise due to a stronger compensatory increase in energy intake; however, this does not hold true when taking energy expenditure into account [22]. Overall, when appropriate actions are taken, chances for optimal weight reduction appear to be equal in both genders.

2.3. Diabetes mellitus

The estimated life expectancy in female diabetic patients is shorter than in men with diabetes [23]; diabetic women with diabetes are also at higher relative risk of developing CV events [24] as they lose their gender-related protection from CVD.

Gestational diabetes is associated with a higher incidence of diabetes and CVD (independently of overt development of T2DM) in later life [25].

2.3.1. Epidemiology

The global prevalence of diabetes among adults aged 18+ rose from 4.7% in 1980 to 8.5% in 2014 [26], with 85–90% due to T2DM. While more prevalent in men, there are more women living with diabetes worldwide, particularly in older-age groups. Gestational diabetes has also been on the rise, affecting 4–9% of pregnant women.

2.3.2. Pathophysiology

Manifestation of diabetes mellitus, especially T2DM, is modified by hormonal changes in women reflected during pregnancy and after the menopause when insulin resistance increases with a consequent increase in the incidence of T2DM including its metabolic and vascular burden.

In addition, elevated triglycerides as one of the key risk factors for developing T2DM seem to play a greater role in women [27]. Occupational stress appears to have a greater impact on the development of T2DM in women [28]. Physical inactivity during leisure time has been identified as an independent and more robust risk factor critical for T2DM development and consequences in women [29]. Inflammatory markers such as C-reactive protein and interleukin 6 have also been found to be associated with an increased risk of T2DM in women, but not in men [30].

Adverse changes in metabolic and vascular risk factors in pre-diabetes are greater in women, the transition from normoglycemia to impaired glucose tolerance and overt diabetes mellitus may be more harmful in women than in men [31]. There are gender differences in diabetic patients regarding the attitudes and beliefs about the disease (Table 2) [24].

2.3.3. Prevention and management of diabetes

Several trials have shown a substantial reduction in the rate of conversion from impaired glucose tolerance to T2DM with lifestyle intervention. Patients at increased risk for T2DM, particularly those with modifiable risk factors (e.g., overweight/obesity, physical inactivity, hypertension, dyslipidemia, pre-diabetes, and smoking), should be intensively educated about the disease with the aim to initiate non-pharmacologic treatment [32]. Women with non-modifiable risk factors such as a family history of diabetes or having delivered a baby weighing >4 kg should also be educated. In addition to the widely recognized risk factors of T2DM, elevated triglycerides, physical inactivity and occupational stress should be considered.

Women diagnosed with gestational diabetes should have lifelong screening every 3 years, overweight or obese women with one or more additional risk factors for diabetes (first-degree relative with

Table 2
Psychosocial and coping characteristics of women with type 2 diabetes mellitus.

Compared with men, women with type 2 diabetes mellitus, generally
• Experience more diabetes-related distress and a poorer sense of wellbeing
• Rate their health-related quality of life higher
• Are at higher risk of developing depression
• Experience more rapid deterioration of physical fitness
• Have less physical activity
• Have higher expectations of the benefits of self-management
• Are more aware of pharmacologic and non-pharmacologic management of type 2 DM
• Exert more effort and employ more strategies to cope with type 2 DM (e.g., religion, active coping, distraction)
• Are influenced less by symptoms of hypoglycemia and hyperglycemia
• Have more physician visits
• Perceive more support from their health-care team and influenced more by their physician
• Believe they have little family and social support and are minimally influenced by such support

DM, diabetes mellitus.
Adapted from Tenzer-Iglesias [23].

diabetes, high-risk race/ethnicity, history of CVD, hypertension, low HDL-cholesterol, elevated triglycerides, polycystic ovary syndrome, physical inactivity) should be tested for diabetes or pre-diabetes from 45 years of age onward at a minimum of 3-year intervals [32].

Regarding diabetes management, the same approach applies to women and men, i.e., tight glucose control at a younger age and a less aggressive approach in the elderly. The preferred drug to initiate treatment in T2DM is metformin; initial insulin therapy should be used in type 1 diabetic patients and considered in newly diagnosed T2DM patients who are symptomatic or have an HbA1c ≥ 86 mmol/mol or blood glucose ≥16.7 mmol/l [33]. In patients with T2DM and manifest CVD, the use of a sodium-glucose cotransporter-2 (SGLT-2) should be considered early in the course of the disease to reduce CV and total mortality [3]. SGLT-2 s have a similar effect in women, but their safety during pregnancy has not been tested to date. There are a number of new drugs to be used in T2DM; however, to discuss their use is beyond the scope of this review.

A key strategy to lower CVD in patients with both types of diabetes is lipid lowering. Therefore, statin therapy is recommended in all patients >40 years of age and in selected younger patients. Renin-angiotensin-aldosterone system blockers are recommended for the treatment of hypertension in diabetes, particularly in the presence of increased urinary albumin excretion [3].

To summarize, management of diabetes mellitus in women should focus more on psychosocial and lifestyle factors.

2.4. Dyslipidemia

2.4.1. Epidemiology

The prevalence of dyslipidemia is very high, 30–40%, despite its substantial decrease in most European countries over the past few decades [34]. While the prevalence of dyslipidemia is lower in women, the rates of its awareness, treatment, and control are higher.

Changes of main lipid parameters in women are frequently associated with their hormonal status or hormonal treatment (Table 3). Chronological aging and hormonal changes at menopause are most likely the main causes of increasing prevalence of dyslipidemia in postmenopausal women. Likewise, LDL cholesterol and triglycerides increase substantially during pregnancy. Polycystic ovary syndrome, as an example of non-physiological changes, is associated mostly with mixed dyslipidemia and insulin resistance. Newer contraceptives have been shown to exert a neutral effect on plasma lipids except for women with central obesity in whom their use could deteriorate the lipid profile. Subclinical hypothyroidism as a frequent cause of secondary dyslipidemia, especially in post-menopausal women, should be ruled out in this population.

Table 3
Association between changes of main lipid parameters and hormonal status in women.

	Menarche/puberty	Pregnancy	Menopause	Hormonal contraception
LDL cholesterol	↔	↑	↑	↔ ↑[a]
Triglycerides	↓	↑	↑	↑
HDL cholesterol	↑	↔	↓	↔

[a] To be avoided in women with metabolic syndrome/central obesity because of increase in LDL cholesterol.

2.4.2. Pathophysiology

Increased levels of atherogenic lipids are caused by genetic and environmental factors and their interaction both in women and men, with the primary etiological factor for atherosclerosis development being elevated LDL cholesterol reflecting an increased number of atherogenic LDL particles. In addition, high concentrations of triglycerides reflecting higher concentrations of remnant lipoprotein particles might be a complementary lipid risk factor for atherogenesis, especially in women. Admittedly, this finding is derived from prospective observational studies with no clinical interventional trials to confirm the causality. While a hotly debated issue, the role of high/low HDL cholesterol as an independent risk factor remains subject to controversy.

2.4.3. Management

As women are still underrepresented in most primary and secondary prevention studies of CVD of atherosclerotic origin, recommendations for the management of lipids in women are extrapolated from data obtained in men. In secondary prevention, the same goals (including aggressive LDL cholesterol lowering to below 1.8–1.3 mmol/l) apply to both sexes.

Supportive data for intensive lipid-lowering treatment in women are based on similar beneficial effects documented for both genders in randomized clinical trials focusing on aggressive lowering of LDL cholesterol using a combination of simvastatin and ezetimibe (28% of women included) [35] and the proprotein convertase subtilisin kexin 9 (PCSK9) inhibitor evolocumab (21% of women included) [36]. Women with dyslipidemia, particularly those with co-existing diabetes, are less likely to be treated with statins.

The benefit of lipid-lowering treatment, mostly with statins, in primary prevention in women is not well established. This may be due to the lower baseline risk and underrepresentation of women in primary prevention trials thus reducing the statistical power to detect moderate treatment effects [37]. Nevertheless, in a 2013 Cochrane review focusing mainly on primary prevention, similar reductions of all-cause mortality, vascular events and revascularizations with statins were observed in women and men [38]. Moreover, in a more recent, robust meta-analysis of statin studies including primary prevention ones, a similar relative benefit of lipid−/LDL-lowering therapy in men and women was reported [39]. Lipid-lowering drugs including statins should not be given when pregnancy is planned, during pregnancy or subsequent breastfeeding. As an exception in individual cases, bile acid sequestrants may be considered. Additionally, in familiar hypercholesterolemia homozygotes and in women with extremely elevated triglycerides, LDL apheresis and plasmapheresis, respectively, are to be considered during pregnancy. Treatment with pravastatin as a drug potentially preventing preeclampsia is recently being investigated [40].

To summarize, the main lipid risk factor in women is LDL cholesterol. In theory, more aggressive treatment of elevated triglycerides, achieved mostly by lifestyle measures, could be more beneficial in women. The cornerstone of lipid-lowering management are statins, potentially combined with ezetimibe; novel drugs such as PCSK9 inhibitors seem to have the same beneficial effect in women as in men. Lipid-lowering therapy is recommended in secondary prevention and in high-risk women in primary prevention, with the same target levels as in men.

2.5. Hypertension

Hypertension is the most prevalent cardiovascular disorder affecting 30–50% of the adult population. It is also a strong risk factor increasing the risk of developing CHD, stroke, peripheral arterial disease, aortic aneurysm, heart failure, chronic kidney disease and atrial fibrillation [41]. The latest systematic analysis for the Global Burden of Disease Study 2017 identified hypertension as the leading risk factor responsible for the largest number of all-cause death [42]. The burden of hypertension is greater for women than men as more women develop adverse pathological consequences. The female gender has been associated with an increased risk of abdominal aortic aneurysm rupture [43].

2.5.1. Epidemiology

At a younger age, hypertension is less prevalent in women but there is a steeper increase in systolic BP in women around the menopause and thereafter, resulting in a higher prevalence of hypertension in elderly women.

In younger individuals, there is generally a greater chance of secondary hypertension whereas most adults have essential hypertension. Fibromuscular dysplasia occurs predominantly in women (>90% of cases) it should be suspected particularly in young girls and women presenting with acute-onset, severe hypertension.

Oral contraception is associated with a small increase in BP in most users and may induce overt hypertension in about 5%. The increase in BP was seen in combined pills but not in those containing progesterone only. Preparations with a low estrogen content (<30 μg) appear to be safe. Hypertension is mild in most cases and BP normalizes in over 50% of women upon oral contraception withdrawal. Oral contraception should only be prescribed in women with well-controlled BP, aged <35 years and non-smokers [44].

Hypertensive disorders complicate 5–10% of pregnancies and are associated with increased maternal, fetal and neonatal mortality. Gestational hypertension, and pre-eclampsia in particular, were found to be associated with an increased risk of developing hypertension, stroke, CHD and venous thromboembolism later in life [45]. Lifestyle modifications are recommended to avoid complications in subsequent pregnancies and to reduce maternal cardiovascular risk [46]. Blood pressure and metabolic factors should be checked annually.

Pre-eclampsia and hypertension in pregnancy were newly found to be strongly predisposed to peripartum cardiomyopathy [46].

2.5.2. Pathophysiology

The pathophysiology of the increase in systolic BP with aging after the menopause in women is quite complex [47]. There is a decrease in estradiol and an increase in testosterone in the menopause resulting in a change of the estrogen-to-androgen ratio. These hormonal changes result in endothelial dysfunction and an increase in body weight or, possibly, T2DM. Sympathetic activation may enhance renin release thus increasing angiotensin II. Endothelial dysfunction is also associated with a reduction in nitric oxide and an increase in endothelin, both contributing to salt sensitivity. Angiotensin II and endothelin, and a reduction in nitric oxide and increase in oxidative stress, all contribute to renal vasoconstriction, thus causing hypertension. The increase in arterial stiffness with aging is greater in women thus inducing greater pulse pressure.

Subclinical organ damage such as left ventricular hypertrophy (LVH) is more prevalent in women and associated with a worse outcome. Left ventricular hypertrophy, together with a greater increase in vascular and myocardial stiffness, results in a higher incidence of heart failure with preserved ejection fraction (HFpEF) and a higher risk of developing stroke. A recent analysis from the Campania Salute Network Registry showed that women developing LVH in hypertension lose their gender-related protection from CVD, a phenomenon similar to that seen in diabetes [48].

2.5.3. Treatment

None of the sex and gender differences in the pathophysiology of hypertension has implications for treatment except for hypertension in pregnancy. The response to antihypertensive agents and beneficial effects of blood pressure-lowering appear to be similar in women and men; however, ACE inhibitors and angiotensin-receptor blockers should be avoided in pregnant women and those of child-bearing potential [49].

A subcommittee of the Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery proposed that an intervention at a diameter < 5.5 cm appears indicated in women with abdominal aortic aneurysm [50].

3. Conclusion

>50% of the decline in CHD mortality is attributable to changes in CV risk factors. There are important gender differences in the prevalence and awareness of major modifiable risk factors. Smoking and diabetes seem to be more harmful in women. Development of LVH and hypertension in women is associated with loss of their gender-related protection from CVD. Women are at a higher risk of developing HFpEF and stroke.

4. Future perspectives/knowledge gaps

Control of major CVD risk factors is worse in women and should be improved. The higher CV risk of smoking and hypertension in women is not reflected in the current assessment of total CV risk. The question arises whether drug treatment of hypertension and diabetes should not be initiated at thresholds lower than in men. So far, the only gender difference in treatment is the suggestion to intervene abdominal aortic aneurysm at a smaller diameter than in men.

Women are still underrepresented in large clinical trials, thus the majority of recommendations for management of the major risk factors is derived from results obtained mostly in men.

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Authorship

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Declaration of interest

None.

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