

Type 2 diabetes and cardiovascular disease in women

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Abstract Cardiovascular disease is the leading cause of death in both men and women. This is also true for patients with diabetes. In general, differences between the sexes are present in several areas, such as epidemiology, pathophysiology, diagnostics, treatment response and prognosis, as well as the way in which disease is experienced and expressed. Cardiovascular disease presents later in life in women, who are therefore more likely to suffer from comorbidities. However, this age-related difference is attenuated in women with diabetes, who suffer their first myocardial infarction at about the same age as men with diabetes. Diabetes mellitus increases the risk of cardiovascular disease by three to four times in women and two to three times in men, after adjusting for other risk factors. This paper describes the differences in cardiovascular disease in men and women and the special situation of women with type 2 diabetes when it comes to risk factors, symptoms and the setting of acute coronary syndromes. Furthermore, it highlights the importance of sex-specific analyses in clinical research to improve our knowledge of cardiovascular disease in women in general and in women with diabetes in particular. The importance of taking sex into account when treating women and men at risk of cardiovascular disease is discussed.

Keywords Cardiovascular disease · Diabetes · Epidemiology · Mortality · Review · Risk factors · Sex · Women

Abbreviations

Apo	Apolipoprotein
CVD	Cardiovascular disease
SCORE	Systematic COronary Risk Evaluation
WHI	Women's Health Initiative

Sex aspects in cardiovascular disease

Despite a remarkable improvement in life expectancy and a decline in cardiovascular mortality during the last few decades, cardiovascular disease (CVD) is still the leading cause of death in men and women (Fig. 1) [1]. It is estimated that CVD causes 35% of all mortality in the world [1] and 48% of all deaths in Europe [2]. The major causes of CVD are ischaemic heart disease and stroke. Ageing populations and improved CVD survival will increase morbidity and step up the demands imposed on healthcare systems in the future. CVD has traditionally been perceived as a male illness but, in Europe—with the exceptions of France, the Netherlands and Spain—at least, it ends the lives of as many women as men [2], and worldwide, CVD is the most common cause of death in women in most countries except for Africa, especially above 60 years of age [3]. The ongoing global epidemics of obesity and diabetes will further accelerate this problem [4]. Women's health has traditionally focused on matters related to sexual and reproductive health. The lack of awareness of CVD in women, among both clinicians and women themselves, is especially alarming in countries with low or intermediate incomes, where public-health policy has largely focused on infectious diseases in general and the maternal and reproductive health of women in particular.

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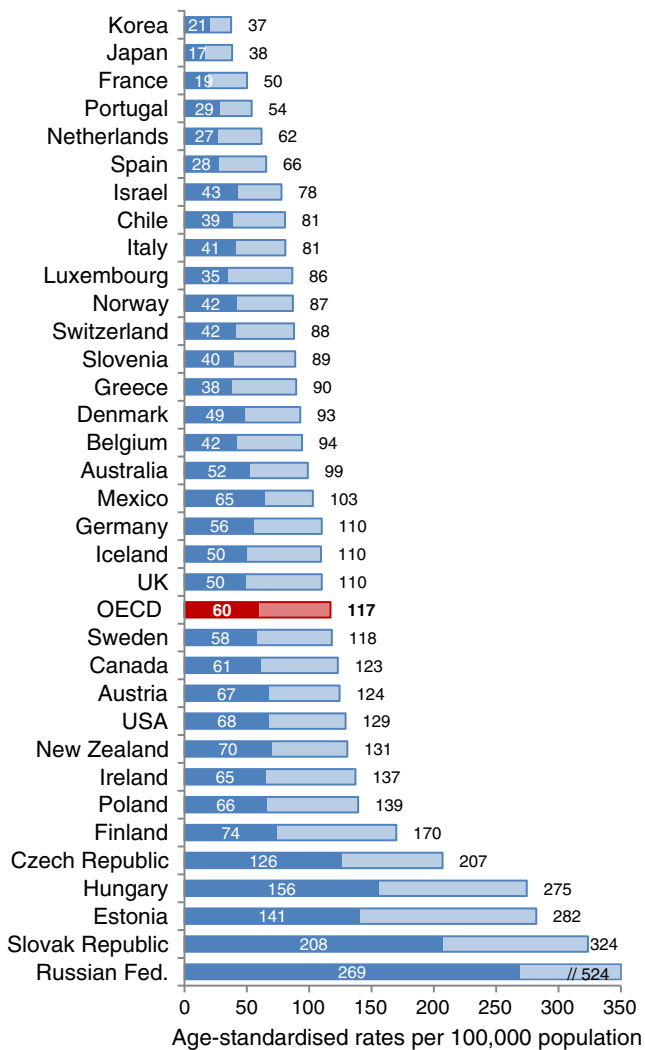


Fig. 1 Mortality rates for ischaemic heart disease, 2009 (or the nearest year), in men and women. Reproduced with permission from [1]. Dark blue, women; light blue, men. OECD, Organisation for Economic Cooperation and Development (countries)

Another important fact is that as many as six in every ten deaths from CVD are related to modifiable risk factors, even among women [3]. It is therefore critically important that we increase the awareness of the sex aspects of CVD among healthcare providers and the general public. There are, for example, sex differences in the impact of conventional risk factors and in the presentation of an acute coronary event. It is particularly important that the situation of women with diabetes is communicated so that events can be prevented more effectively. Even though the cardiology community has increased attention on women with CVD during the last 10 to 15 years, using campaigns such as ‘Go red for women’ and publishing sex-related guidelines [5–7], the evidence to support the treatment of heart disease in women remains incomplete [8, 9] and

awareness is still not optimal. In Sweden, a survey from 2006 at the start of the Swedish ‘Go red’ campaign revealed that about 18% of the 1,000 participants recognised CVD as the main killer in women. In March 2012, the same type of survey initiated by the Swedish Heart and Lung Foundation reported that this figure had increased to 40%, although 60% did not know [10].

By systematically increasing sex-specific analyses in future cardiovascular research, our knowledge and understanding of the differences between the sexes in terms of epidemiology and treatment will increase. This article discusses the particular risk seen in women with type 2 diabetes. For information on women with type 1 diabetes, we recommend the update by Nadeau and Reusch [11].

Diabetes and CVD

People with diabetes run a high risk of CVD and mortality, and CVD is a major cause of death [4, 12]. There has been a welcome decline in CVD deaths in both men and women in Western Europe and North America in recent decades, but the same trend has not been seen in Central or Eastern Europe [2, 13, 14]. However, this decline has not been observed to the same extent in people with diabetes [15, 16], and some studies [15, 16], but not all [17], report that this is particularly the case for women with diabetes. The longer life expectancy in general might be one explanation. In Sweden, life expectancy has increased in people with diabetes [13], and a recent report from the USA showed a significant improvement in the estimated 10-year risk of CHD among adults with diabetes [18]. A large number of the global adult population suffer from glucose abnormalities, and the global trends indicate an increase in prevalence of epidemic proportions [4]. Ageing populations and lifestyle changes, with increased obesity, reduced physical activity and changes in dietary habits, are some of the explanations. This epidemic will not only have diabetes-related impacts on personal lives and healthcare costs, it will also have a major effect on the future panorama of CVD and healthcare. The global prevalence of individuals living with diabetes is expected to increase from about 8.3% in 2011 to 9.9% by 2030 [4]. Moreover, a large number of people with undiscovered diabetes or impaired glucose tolerance also run an increased risk of future CVD mortality [19, 20]. According to the most recent Diabetes Atlas [4], women account for about 50% of people living with diabetes. There is no clear evidence that the prevalence of diabetes differs between men and women, despite a reported male-to-female ratio varying widely between different countries and ethnic groups.

Impact of CVD risk factors in men and women with and without diabetes, and the sex gap

According to the INTERHEART study report from 2004, nine factors are responsible for 90% of all myocardial infarctions [21]. One of these is diabetes and the others are dyslipidaemia, hypertension, smoking, psychosocial stress, obesity—especially abdominal fat—physical inactivity, poor eating habits with too little fruit, and high alcohol intake. Diabetes increases the risk of CVD and mortality by two to four times. However, diabetes has a different impact in women and men; it increases the risk by about four times in women and about twofold in men [21, 22]. The combination of several risk factors further enhances the risk [21, 22] and such combinations are common in patients with type 2 diabetes, who often have a cluster of risk factors related to the metabolic syndrome. CVD presents about 10 years later in women than in men [23], but this age gap is almost completely attenuated when diabetes is present; it is therefore possible to conclude that women with diabetes lose their normal ‘female’ protection from CVD. One consequence is that women with diabetes suffer myocardial infarctions several years earlier than women without diabetes and thus approaching the same age of onset for myocardial infarction as men [13, 15, 22].

These findings of increased cardiovascular risk in women vs men with diabetes have been interpreted in contradicting ways by different investigators and have been extensively analysed and discussed, for example, in meta-analyses by Huxley et al, Kanaya et al and Orchard [22, 24, 25]. Some did not find an increased risk while others found an increased risk solely related to increased risk-factor burden and comorbidity in women compared with men with diabetes. Others found that increased risk remained in women with diabetes, even after adjusting for other risk factors. In the meta-analysis by Huxley et al, the increased age-adjusted relative risk of CHD was more extensively reduced in women, from 3.69 to 3.12, compared with men, in whom it fell from 2.16 to 1.99, after adjusting for multiple risk factors such as hypertension, lipid abnormalities and weight [22]. Accordingly, even after adjustment for a more severe cardiovascular risk profile, they found a somewhat higher remaining risk of CVD in women than in men with diabetes. Thus, sex itself might be a contributor, a fact that needs to be further confirmed and understood. However, the authors also discussed the possible explanation of less aggressive preventive treatment in women with diabetes. When it comes to absolute cardiovascular event rates at younger ages, the numbers are higher in men compared with women, regardless of whether or not they have diabetes [13, 26–28].

The reasons for the lower risk of CVD in women without diabetes at younger ages and the reason why this protection is attenuated when women develop diabetes are still not

understood and might be a clue to understanding the differences in the age distribution of CVD between the sexes. One important factor might be sex differences in the impact of insulin resistance, which also appears to be differentially influenced by age, sex hormones and lifestyle factors in men and women [28, 29]. Another reason might be a difference in the impact of existing and clustering risk factors, including hormonal levels [23, 30]. In fact, the sex difference for age at first myocardial infarction in the general population has largely been explained by the higher levels of risk factors at younger ages in men compared with women [23], such as blood lipids, smoking and family history. Indeed, a recent paper in *Diabetologia* reported that the insulin-resistant state attenuated the otherwise more favourable risk profile seen in women without diabetes [31]. The role of sex hormones in this context needs to be explored more closely.

In women, risk factors considered to be related to early CVD in the absence of known diabetes are polycystic ovary syndrome, premature menopause, gestational diabetes and hypertension, as well as a history of pre-eclampsia [32, 33]. Recently, lactation has emerged as a factor related to CVD: a longer lactation period appears to have a protective effect when it comes to future CVD [34]. A sex analysis from the INTERHEART study found that several risk factors (such as hypertension, diabetes, high alcohol intake and low physical activity) were stronger in women than in men. Diabetes, current smoking, hypertension, apolipoprotein (apo)B/A levels, smoking and hypertension were more strongly associated with myocardial infarction in women below the age of 60 compared with older women [23]. Increased LDL-cholesterol levels are related to CVD in both men and women, but low HDL-cholesterol and increased triacylglycerol levels have been shown to be more strongly related to CVD in women than in men [35]. The Women’s Health Study recently reported that, in the presence of a low total-atherogenic-particle burden, as defined by an apoB100 level <0.90 g/l, few CV events occurred and there was no remaining association between CV events and HDL-cholesterol level [36]. Unfortunately, only a small percentage of the women had diabetes, but diabetes was more common among those who, despite high HDL-cholesterol levels, had a CV event. In general, women from a young age to menopause have lower LDL-cholesterol levels and higher levels of HDL-cholesterol and apoA-I than men [37]. However, on entering the menopause, women’s total and LDL-cholesterol levels increase to higher levels than in men [30, 37]. The typical lipid profile in patients with type 2 diabetes is normal or there are low levels of LDL- and HDL-cholesterol and increased triacylglycerol levels. Sex differences in lipid profiles when diabetes is present are less well explored but, regardless of this, both primary and secondary intervention trials significantly reduce CVD in men and women with diabetes and with at least one cardiovascular risk factor [38–40].

Importantly, as discussed above, when it comes to women with known diabetes, the risk of CVD is increased even after taking account of other risk factors [22]. This indicates that the diabetes itself is extremely important in women. The risk-score system from the Framingham study [41] and in Europe, the Systematic COronary Risk Evaluation (SCORE) system [42] use classic risk factors for the evaluation of CVD risk. In patients with diabetes, the UKPDS risk engine is available [43]. Both the Framingham study and the European SCORE system have limitations in women aged 65 years or older, and underestimate the true risk for elderly women. The diabetes UKPDS engine has the advantage of including important diabetes-related factors known to increase the risk of CHD, such as glucose control and duration of diabetes. However, even the UKPDS risk engine is based on a diabetes population under 65 years of age, and might therefore underestimate the true risk for elderly women. Furthermore, it is important to remember that female sex is rated as a beneficial risk factor in comparison with male sex in the UKPDS engine, and the engine therefore fails to take account of the considerably increased risk women with diabetes run in relation to women without diabetes. The recently developed Reynolds Risk Score [44] is an attempt to improve risk-score systems in women, but further validation is needed in women with diabetes.

Psychosocial stress is nowadays a well-known independent risk factor for CVD. In the INTERHEART study, 30% of CVD risk was attributed to stress. Clinical experience shows that psychosocial stress has a different impact on CVD risk in women compared with men [45, 46], examples being that family stress is a stronger risk factor for CVD for women than for men, and that broken heart syndrome (takotsubo)—the ultimate manifestation of stress, leading to a particular form of acute heart failure—almost only occurs in women. Furthermore, some studies have reported that psychosocial work stress is independently linked to a higher risk of future type 2 diabetes, with the effect being consistently higher in women than in men [47]. Also, work stress has been linked to future weight gain in obese men in contrast to a link with weight loss in lean men. A recent sex analysis from the White Hall II study showed that sex and body-weight status play a critical role in determining the direction of the association between psychosocial stress and future type 2 diabetes, and that work stress is associated with a lower risk of type 2 diabetes among non-obese men, but with a higher risk of diabetes among obese women [48].

Glucose as a risk factor for CVD

Blood glucose level is currently regarded as a continuous risk factor for CVD; not only people with overt diabetes run an increased risk of future CVD, but also people with

slightly elevated fasting or postprandial glucose levels [19, 20]. It appears that post-load glucose levels are even more important than fasting glucose levels in terms of future cardiovascular mortality, at least in men [20]. One major drawback from a sex perspective is that several of the older observational trials involving glucose levels and future CVD in groups primarily included men: the Helsinki Policemen's Study; the first Whitehall Study; the Paris Prospective Study; and the Honolulu Heart Programme. As a result, the related meta-analyses include only a small number of women [19]. From the Framingham offspring data, it was recently reported that slightly elevated fasting glucose levels (impaired fasting glucose) were shown to be an even stronger predictor of CHD in women than in men and were almost as strongly predictive as diabetes. The question of whether lower cut-off points for fasting should be used in women in order to diagnose diabetes or impaired fasting glucose was consequently discussed [49]. It is necessary to analyse whether different cut-off points for men and women could also be extended to other risk factors, such as BMI and hypertension, as is already the case when it comes to HDL-cholesterol and triacylglycerol levels. In addition, the above discussion of stronger risk factors in younger women further underlines the importance of this question.

One major problem is that impaired glucose tolerance and type 2 diabetes often remain silent and are first discovered at the time of a cardiovascular event. In fact, when an OGTT is performed in non-diabetic patients with a myocardial infarction, as many as two-thirds are found to have impaired glucose tolerance or diabetes [50–52]. A sex analysis in the Euro Heart Survey on diabetes and the heart revealed a higher prevalence of glucose abnormalities in women than in men and only 19% of the women and 27% of the men with coronary artery disease had normal glucose regulation when tested with an OGTT [53]. These previously undiscovered glucose disturbances are also adversely related to outcome of myocardial infarction [54, 55]. In the recent report on HbA_{1c} levels in the INTERHEART study [56], self-reported diabetes did indeed underestimate the true prevalence of dysglycaemia. Furthermore, after adjusting for the nine known risk factors applied in the study (including diabetes and sex), HbA_{1c} remained a progressive independent predictor of myocardial infarction in patients with and without diabetes and was related to increased risk in both men and women (OR for men 1.38 [95% CI 1.32, 1.43] and for women 1.45 [1.36, 1.56]). Diabetes was an even stronger risk factor in women, especially those under the age of 60 [23].

To the best of our knowledge, the question of whether improved glucose levels and the use of different glucose-lowering substances have a different impact on CVD in women and men has not been extensively analysed, but performing sex-specific analyses of this kind could be of interest in the

glucose intervention trials that are currently in progress. In the original paper from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, in which 38% of participants were women, there were no differences in the effect of intense glucose control on mortality or the primary endpoint between men and women ($p=0.92$ and $p=0.74$, respectively) [57]. Neither was there in the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) trial, in which 42% were women, any heterogeneity between men and women ($p>0.10$ for heterogeneity) [58]. In the post-myocardial infarction trial Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) 2, wider sex-specific analyses were performed; these failed to reveal any differences in the effect of the randomised treatment, but did identify different risk-factor profiles in women and men and, in general, a heavier risk-factor burden in women. The presence of diabetes complications was, in particular, a negative predictor for CVD after myocardial infarction in women [59].

Sex-specific conditions in women

Several women-specific conditions can complicate and influence the risk of future CVD, such as polycystic ovary syndrome, premature menopause, gestational diabetes and history of pre-eclampsia. In pregnant women with diabetes, type 1 or type 2, the risk of accelerating diabetes complications is another obvious risk, in addition to the risk of fetal malformation. Planned pregnancy with optimised glucose control is important for both the child and the mother. However, the risk also extends to women with elevated glucose levels during pregnancy, as recently shown in the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study [60]. Up to 18% of pregnant women without known diabetes could have gestational diabetes if tested with an OGTT. New proposed guidelines from the International Association of Diabetes and Pregnancy Study Groups (IADPSG; www.iadpsg.org) on diagnostic criteria and screening for gestational diabetes have been published recently and aim to predict an adverse pregnancy outcome for the child and the mother [61, 62]. For the mother, it is not only the risk of future diabetes that is present but also an increased risk of CVD. A recent report from Canada indicates that women with gestational diabetes run a particularly high risk of future CVD and a substantial part of this risk is attributed to the subsequent development of type 2 diabetes, highlighting the importance of diabetes prevention in this group [63]. Consequently, the prevention of weight gain and abdominal obesity after pregnancy appears to be very important as, particularly in younger women, these risk factors are related to future CVD.

In women with diabetes or polycystic ovary syndrome, there is a hormonal imbalance in androgen and oestrogen

levels, and sex hormones appear to influence glucose control in women with diabetes [64]. Promising experimental research results, including the positive effects of oestrogen on endothelial function [65] and the obvious clinical relief of typical menopausal symptoms, were the basis of previously extensive use of sex-hormone-replacement therapy in postmenopausal women. Randomised intervention trials with hormone replacement, such as the Heart and Estrogen/Progestin Replacement Study (HERS) and the Women's Health Initiative (WHI) trial, did not, however, show any beneficial effects on CVD, but instead indicated a slightly increased risk of thrombo-embolic events and breast cancer [66]. The question of whether treatment with hormone-replacement therapy was started too late after menopause has since been discussed. No specific diabetes data have been presented in the WHI studies. In overall terms, the use of postmenopausal hormone therapy has decreased markedly [67].

Acute coronary syndromes in women and diabetes

There has been a substantial improvement in outcome after myocardial infarction in patients with and without diabetes during the last few years. The results from the Swedish register of coronary care (RIKS-HIA, SWEDEHEART), which includes almost all patients admitted to coronary care units in Sweden, showed an absolute reduction in the 1-year mortality rate after myocardial infarction of 10% from 1995 to 2002 in patients with diabetes (from 29.7% to 19.7% compared with 16.6% to 12.1% in those without diabetes in 1995–2002) [68] and further improvements are seen every year. Enhanced coronary care, the improved use of evidence-based treatment, such as lipid-lowering treatment and early coronary revascularisation, as well as improved risk-factor management before myocardial infarction are some explanations. However, diabetes is still an independent predictor of adverse outcome and the mortality gap after a coronary event between patients with and without diabetes increases with follow-up time, even after modern treatment techniques, such as percutaneous coronary intervention with a stent [69].

Back in 1988, data from the Framingham cohort revealed that women with diabetes had a poorer outcome after myocardial infarction than men [70]. Older myocardial infarction trials recruited, due to inclusion and exclusion criteria, limited numbers of patients with diabetes and even smaller numbers of women with diabetes, and this has hampered knowledge of the best treatment strategies for this group. In sex-specific analyses (Fig. 2) from our group reveal that at age under 65 years, women with diabetes had the poorest outcome after a coronary event, even worse than men with diabetes [71], a finding that was not apparent before the sex-stratified analyses. The increased risk was explained by an elevated burden of risk factors, including hypertension, heart failure and smoking, that

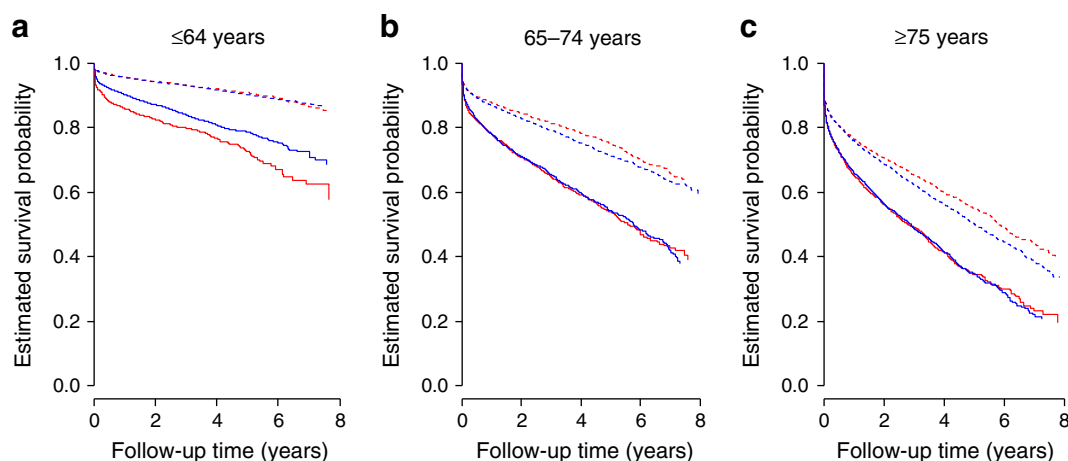


Fig. 2 Analyses of mortality after myocardial infarction in patients with diabetes in Sweden (RIKS-HIA, SWEDHEART) in 1995–2002, by sex. Adapted from [71]. $n=70,882$; 31% women; 21% with diabetes mellitus. **a** Age ≤ 64 years, RR for women with diabetes 1.35 (95% CI 1.18, 1.54) and women without diabetes 0.96 (95% CI 0.86, 1.07); (**b**) age 65–74 years, RR for women with diabetes 0.99 (95% CI 0.91,

1.08) and women without diabetes 0.88 (95% CI 0.83, 0.94); and (**c**) age ≥ 75 years, RR for women with diabetes 0.96 (95% CI 0.89, 1.04) and women without diabetes 0.87 (95% CI 0.83, 0.91). Red broken line, non-diabetic women; red solid line, women with diabetes; blue broken line, non-diabetic men; and blue solid line, men with diabetes

was already present at admission and was not related to sex itself or to any major differences in evidence-based treatment. Despite this, treatment with ACE inhibitors was shown to be less common in women with diabetes after adjusting for other risk factors. Further evaluations are needed to explain why these younger women with diabetes more commonly had an excess of risk factors at admission compared with men with diabetes and women without diabetes. The higher risk-factor burden at admission may be the natural result of sex-related vulnerability to risk factors in younger women, and women with diabetes and glucose disturbances appear to have more adverse metabolic disturbances than men [22, 23, 52, 72–74]. Whether earlier and more aggressive risk-factor intervention in women with diabetes can prevent CVD complications needs further evaluation. One possible explanation for the higher prevalence of heart failure could be a sex difference in previous undiagnosed heart failure or previous silent myocardial ischaemia. It is claimed that women, and especially women with diabetes, suffer more frequently from heart failure with preserved ejection fraction ('diastolic dysfunction'), a condition known to be widely undiagnosed in the general population [75]. Furthermore, symptoms of myocardial ischaemia might more frequently be atypical in patients with diabetes as a result of autonomic dysfunction and a lower perception or lack of pain, resulting in only tiredness and breathlessness [76]. For this reason, there is a risk of undiagnosed previous silent myocardial infarctions and coronary ischaemia in patients with diabetes. One result might be fewer referrals for investigation and less aggressive treatment, with fewer revascularisations.

In general, there appears to be a sex difference in the presentation of symptoms and the way women and men express their symptoms. Men more frequently describe chest pain, left arm pain or diaphoresis, while women more commonly describe nausea, tiredness and jaw pain, although the opposite may occur. The difference in the occurrence of chest pain has been related to women's older age and the presence of diabetes [77]. Consequently, it could be assumed that women with diabetes more frequently experience atypical or silent myocardial infarction. One other important difference between women with and without diabetes and acute coronary syndrome is the extent of atherosclerosis and stenosis of the coronary arteries. Women with diabetes more frequently have significant stenosis in all three coronary arteries, to the same extent as men with diabetes, while women without diabetes more frequently have non-obstructive coronary artery disease [78].

Medical treatment and early revascularisation after an acute coronary event have consistently shown at least the same impact in patients with diabetes as in those without diabetes [68, 79]. Without further knowledge and until this subject is better explored, it can be assumed that this finding could be extended to women with diabetes, and approaches to primary and secondary prevention should be based on updated guidelines [6, 79].

Summary and future directions

Diabetes is a strong risk factor for future cardiovascular complications and in women diabetes attenuates the usual female advantage. Unfortunately, there appears to be a heavy risk-factor burden in women with diabetes, and

younger women appear especially sensitive to CVD risk factors. An increase in the use of primary and secondary preventive measures to reduce the risk-factor burden and prevent or postpone coronary events is important. Aggressive multifactorial risk management, including lifestyle changes, has been shown to be important in reducing cardiovascular morbidity and mortality in patients with diabetes [80], and earlier diagnosis of coronary artery disease, before the onset of myocardial complications, is recommended. During pregnancy, gestational diabetes could easily be discovered and, if identified, the woman should be followed more intensively for the rest of her lifetime because of the risk of future CVD and diabetes. Cardiologists should be encouraged to include women's health issues, such as pregnancy complications and use of birth control, when taking medical histories and assessing cardiovascular risk. As trials in patients with myocardial infarction have recruited a limited number of patients with diabetes and an even smaller number of women with diabetes, our knowledge of the most effective treatment and preventive strategies is limited. More research on the impact of sex in diabetes and CVD is needed, together with an awareness of the need to include sufficient numbers of women, as advocated by international guidelines [5–7]. For both men and women, it is important to have more sex-based knowledge of diabetes and CVD.

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Contribution statement Both authors were responsible for the conception, design and drafting of the manuscript, and approved the final version for publication.

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