Cardiovascular disease prevention and therapy in women with Type 2 diabetes

Cardiovascular Disease prevention and Therapy in women with Type II diabetes

Camilla Cocchi[a], Francesca Coppi[b], Alberto Farinetti [c], Anna Vittoria Mattioli[a,d] *

Affiliation:

a) Istituto Nazionale per le ricerche cardiovascolari U.O. Modena, Italy

b) Cardiology Division, Policlinico di Modena, Modena, Italy

c) Department of Medical and Surgical Sciences for Children and Adults, University of Modena and Reggio Emilia, Modena, Italy

d) Surgical, Medical and Dental Department of Morphological Sciences related to Transplant, Oncology and Regenerative Medicine, University of Modena and Reggio Emilia, Italy

Running title: diabetic women and cardiovascular

Address for correspondence:

Prof Anna Vittoria Mattioli,
Surgical, Medical and Dental Department of Morphological Sciences related to Transplant, Oncology and Regenerative Medicine
University of Modena and Reggio Emilia,
Via del pozzo, 71 41100 Modena (Italy)
E-mail: annavittoria.mattioli@unimore.it

Word count : 3,802 (without references)

References: 71

Conflicting Interests: None Declared

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors

Author contribution. AVM and AF conceived of the idea at the basis of the article, CC, AVM, FC, AF developed the different part of the manuscript, performed the final supervision. All authors contributed to and approved the final manuscript.

Orcid:

Anna Vittoria Mattioli: 0000-0003-1487-9530

Camilla Cocchi: 0000-0002-4355-6194

Francesca Coppi: 0000-0001-7715-6941

Alberto Farinetti: 0000-0003-2133-3595

Lay Abstract

It is known that despite cardiovascular (CV) disease being the most frequent cause of death in women in industrialized countries, the idea that CV disease affects mainly men and affects women only after menopause still persists. This results in under-diagnosis and under-treatment of cardiovascular disease in women. This phenomenon depends on various factors including the lack of perception of risk in women themselves, the reduced social action of prevention of CV risk factors in women and finally the lower presence of women in the population included in scientific studies.

The condition is also present in women with T2DM who have a high risk of developing cardiovascular disease even before menopause. This review is aimed at exploring the factors that determine an underestimation of cardiovascular risk in women with T2DM. Failure in identifying risk carries a high social and economic cost.

Executive Abstract

CVD in Women with T2DM:

- Cardiovascular disease (CVD) is the primary cause of death among women with T2DM
- The risk of major CV events in women with T2DM is 20-30 years earlier than in women without T2DM.
- The impact of diabetes mellitus on development of coronary heart disease is greater in women
- Women are usually under-diagnosed and may receive delayed diagnosis for CV due to several factors

Lifestyle for prevention of CVD in women with T2DM

- Women are less likely to adhere to healthy lifestyle and therapy

Therapy with SGLT2i in women.

- Some of the new hypoglycemic drugs (GLP-1RAs, and SGLT-2 Inhibitors) have shown efficacy in reducing cardiovascular events in both women and men.
- The presence of women in CV risk clinical trials has consistently remained below 50%. Similarly, women are under-represented in SGTL-2i trials

Abstract

Cardiovascular diseases are the leading cause of death among men and women, although women are usually under-diagnosed and experience a delay in diagnosis. This also occurs in women with T2DM, despite the fact that diabetes is recognized as a major cardiovascular risk factor.

Several factors influence the gap between the diagnosis and the treatment of cardiovascular disease in women: i.e. lack of perception of cardiovascular risk, the effects of sex-related risk factors and the action of drugs in women.

Women with T2DM are more likely to be assigned a lower risk category of CVD and receive lifestyle counseling as well as less intensive CVD therapy compared to men. The present narrative review aims to analyze the risk of CVD in women with T2DM and whether there is a differences between men and women in the efficacy of SGLT-2 Inhibitors, new hypoglycemic drugs.

Key-words: women; diabetes; prevention; lifestyle

List of abbreviations:

CVD=Cardiovascular Disease

DM = Diabetes mellitus

T2DM= Type 2 Diabetes Mellitus

SGLT-2i= SGLT-2 inhibitors

Introduction

According to the AHA statement, at least 68% percent of people age 65 or older with diabetes die from some form of heart disease; and 16% die of stroke. Adults with diabetes are two to four times more likely to die from heart disease than adults without diabetes. [1] In the adult population, diabetes is more prevalent in men than in women. [2] In addition, the peak in diabetes prevalence occurs earlier in men (65– 69 years of age) than in women (70–79 years of age). [3] The NCD Risk Factor Collaboration analyzed data from 146 countries and showed that age-standardized prevalence rates increased more in men (from 4 % to 9%) than in women (from 5% to 8%) between 1980 and 2014. [3] The International Diabetes Federation indicated sex differences in worldwide diabetes prevalence in adult populations (9.1% in men vs 8.4% in women). [4]

However, women with Type 2 Diabetes Mellitus (T2DM) had a greater rate of cardiovascular death and the years of life lost due to the disease are higher (6.8, 6.4 and 5.4 in women vs 6.3, 5.8 and 4.5 in men, all respectively 40, 50 and 60 years old). [5] The risk of major cardiovascular (CV) events in women with T2DM is 20-30 years earlier than in women without T2DM, mitigating the pre-menopausal advantage in the onset of CVD. Atherosclerosis is a long-lasting disease and, according to the newest theories, it begins to develop during fetal life. It is recognized that women who have developed T2DM have an acceleration of atherosclerosis. In addition, changes in the anatomy of plaque occur during women's lives due to the well-known effects of estrogen on the endothelium. [6]

The present narrative review aims to analyze the risk of CVD in women with T2DM and whether there is a difference between men and women in the efficacy of hypoglycemic drugs. As evidenced in cardiovascular disease, women are under-diagnosed and undertreated than men, due to the link between diabetes and CVD, we aim to find out if women with T2DM were equally underestimated than men. We have analyzed the several reasons that underlie differences in the treatment and in the efficacy of drugs in women with T2DM.

CVD in Women with T2DM

Several studies have shown that the impact of diabetes on development of coronary heart disease is greater in women. A meta-analysis estimates a 44% greater RR for incident CHD in women with T2DM compared with men. [7] Similarly, risk of stroke in patients with T2DM is greater in women. [8] These results support the hypothesis that DM leads to a higher relative risk for cardiovascular disease in women. Women with T2DM are more likely to develop CVD resulting in cardiovascular death compared to women without T2DM.

Several reasons contribute to the increase in CVD in women; notably the effects that diabetes has on the vessel wall by inducing vascular remodeling. [8] Elevated glycaemia is a known determinant of both arterial stiffness and carotid intimal media thickness. [9] A meta-analysis reported that an increase in carotid intima/media thickness by 0.13 mm is associated with an increase in CV risk by nearly 40% in patients with T2DM. [10] Moreover T2DM affects microcirculation [10] and T2DM patients show alterations in the vascular extracellular matrix (increased collagen-to-elastin ratio), probably induced by inflammatory and pro-fibrotic changes. [11]

Another reason is related to the different CV risk profile of women with T2DM. Women with T2DM are less likely to achieve target values for systolic blood pressure, LDL and HDL cholesterol, fasting plasma glucose, and HbA1c. Regarding treatment, women are more likely than men to take insulin, either alone or in combination with oral hypoglycemic drugs. [12]

Although ageing induces body composition changes in both sexes, menopause predispose to accumulation of visceral fat. Considering the impact of female sex on risk factors in diabetes, abdominal adiposity plays a central role by affecting insulin resistance. Sexual dimorphism in fat distribution and adipose tissue, skeletal muscle and liver substrate metabolism contributes considerably to sex differences in tissue-specific insulin sensitivity and cardiometabolic health. [13]

The strong relationship between central obesity and diabetes is well known. Obesity increases insulin resistance and glucose intolerance, and the coexistence of obesity and T2DM further increases the risk of CVD. [3, 13]

Obesity and T2DM are associated with a systemic inflammation leading to endothelial dysfunction. [3, 14]

ESC guidelines for diagnosis and management of pre-diabetes and diabetes underline that the addition of circulating biomarkers for CV risk assessment has a limited clinical value. In patients with DM without CVD, measurement of inflammatory markers (i.e. C-reactive protein) adds little incremental value to risk assessment. [15] Furthermore, the differences between women and men have not yet been systematically explored. [15] Diagnostic approach to CVD is similar in women and men with T2DM. However several studies reported some differences between sexes. A resting ECG may detect silent MI in 4% of individuals with DM, which has been associated with increased risk of CVD and all-cause mortality in men but not women. [15, 16] As suggested by ESC guidelines, sex-specific differences in the diagnosis of coronary artery disease require further investigation.

Women at all ages have a lower risk for sudden cardiac death compared to men, but in the presence of DM the risk of sudden cardiac death is quadrupled in both men and women.[15]

While cardiovascular disease (CVD) remains the leading cause of death among men and women, women are usually under-diagnosed and may have a delay in diagnosis. [5]

The gap between the diagnosis and treatment of cardiovascular disease in women depends on several factors: a) the lack of perception of cardiovascular risk which leads to a delay in diagnosis, b) the exposure to risk factors that act differently in women and men, and specific sex-related risk factors which are still little known and, finally c) the possible different action of drugs in women. This also occurs in women with T2DM, despite the broad consensus that diabetes is a major cardiovascular risk factor. [5,17]

Lack of perception of cardiovascular risk

In recent years, physician awareness of cardiovascular risk in women has increased, reducing the impact that led to the under-diagnosis of CVD. [5,18]

However, several studies have shown that the perception of CVD risk in women themselves has not changed. Most women are unaware of the gravity and the frequency of CVDs. There are several reasons for this situation: the lack of research on cardiovascular diseases specifically dedicated to women, insufficient education specifically aimed at women with regard to female-specific CV risk factors, underestimation by the national health system of the prevalence of CVD among women. [19,21,21]

All these factors contribute to invalidate efforts in the field of prevention as well as in encouraging the adoption of healthy lifestyles and therapies. [22,23]

Different exposure to risk factors acting differently in women and men and sex specific risk factors

The exact reasons for the sex differences in risk factors observed here are not known and will depend on many biological and sociocultural contributors. Hypertension is highly prevalent among women, in particular non-Hispanic black women, compared to other groups. Higher BMI and waist circumference in men are likely to contribute to higher blood pressure, cholesterol levels and diabetes prevalence. DM is also a strong risk factor for CVD and heart failure among women. Sex differences in coronary heart disease risk cannot be explained only by estrogen or progesterone levels. The risk of death from coronary heart disease in men is higher than that of women throughout the life span, without flexion in the age-coronary heart disease mortality curve in women at the time of menopause, despite large differences in endogenous estradiol and progesterone levels before and after menopause, nor does postmenopausal exogenous estrogen appear to influence the risk of coronary heart disease. [5,23] Furthermore, sex hormones, such as estrogen and testosterone are likely to contribute to sex differences in blood pressure and in CVD.

Recently, CV risk factors that are unique to women and related to their reproductive history have been studied. The development of CVD in women may correlate with specific events taking place throughout a woman's hormonal history.

Some sex-specific risk factors are related to gynecological history: i.e. natural and surgical menopause, polycystic ovary syndrome, premature ovarian failure. In addition some complications of pregnancy have been identified as risk factors for the development of cardiovascular disease: i.e. gestational diabetes, gestational hypertension and preeclampsia, intrauterine growth restriction and preterm birth. [5,23,24] All these conditions that develop during the fertile period of life or peri menopause may affect the onset, clinical features, and prognosis of CVD later in women's lives and, recently, have been suggested to be early markers of future CVD. The cardiovascular risk stratification in women should also include the assessment of these specific risk factors.

Women who develop gestational diabetes have a higher risk of developing cardiovascular events and type II diabetes over the years. [24,25] A meta-analysis of 675,455 women confirmed that women with gestational diabetes had a significantly higher risk of developing subsequent type 2 diabetes (RR = 7.43 (95% CI: 4.79-11.51).

Women with a family history of type 2 diabetes and developed gestational diabetes were more likely to have CVD risk factors, specifically metabolic syndrome, and to experienced CVD events at a young age. In this group of women, the relative risk was 4.69 within the first five years postpartum and 9.34 beyond the five years postpartum.

Gestational diabetes could be an early biomarker of CVD leading to identify a high risk category of women, suitable for early prevention. [5,24]

The degree to which increased CVD risk associated with several of the female-specific conditions occurs independent of conventional CVD risk factors is unknown. [15]

Different action of drugs used in cardiovascular prevention.

There are sex-related differences in CV medications. Men with T2DM or cardiovascular disease were diagnosed earlier and more often treated with aspirin, statins, and antihypertensive treatments than were women, and were therefore more likely to achieve recommended treatment targets for risk factors. [26,27,28,29] The reason for this is unclear, but might be multifactorial, reflecting different system-related, physician-related and patient-related factors.

Several anatomical and physiological differences between the sexes (body dimension and composition, metabolism, gastric and hepatic differences, renal functions) could influence the activity of many drugs, including interaction with other drugs, bioactive compounds, foods and beverages. [28] Women are less represented in RCT trials (relative to their overall representation in disease populations) and adherence to therapy is consistently lower in women with T2DM compared to men. It is important to consider gender differences in treatment modalities and drug metabolism (sex-specific cytochrome expression). Moreover, even when drugs are prescribed, treatment is often less aggressive and does not achieve optimal goals, i.e. with T2DM women have higher levels of glycated hemoglobin. A major issue is that postmenopausal women are less likely to be treated with statins and aspirin than a man with a similar CV risk.[29]

Several reasons have been evoked to explain this gap, for example, a limitation on the prescription of statins in women seems to be the greater tendency to develop myopathies. [30]

In order to reduce this gap, AHA/ACC primary prevention guidelines for statin initiation included sex in the cohort formula for CVD risk determination. [31]

Adherence to statin prescribing guidelines in patients with previous CVD is still an open question. A recent retrospective study found that only 85.6% of patients diagnosed with CAD have ever received statins and less than 70% maintain adherence to therapy over time. The authors reported that 4 factors play a key role in sex differences in adherence to

statin therapy - age, smoking history, evaluation by a cardiologist and known adverse reactions to statins. [32] However, these suboptimal treatment patterns lead to a higher mortality and poorer CVD outcomes than in men.

The risk of bleeding from aspirin use is similar in men and women, resulting in a 12% reduction in CV events in both sexes, led by a decrease in ischemic stroke in women and myocardial infarction in men. [33,34]

Recent large studies in moderate-risk patients have not confirmed the benefits of aspirin in primary prevention. [35,36] The A Study of Cardiovascular Events in Diabetes (ASCEND) evaluated 15,480 patients with DM without CVD treated with 100 mg aspirin once daily or placebo. They found a significant difference in the primary composite efficacy outcome (MI, stroke, transient ischemic attack, or death from any cause) which occurred in 658 patients (8.5%) treated with aspirin versus 743 (9.6%).) treated with placebo (rate ratio 0.88, 95% CI 0.790.97; P = 0.01). [36]

It has been recently suggested that body weight or size can lower responsiveness to aspirin requiring tailored daily doses. [37] Pharmacokinetic data suggest a lower degree of platelet inhibition, especially in moderate-to-severely obese patients. [38] However, the benefit of intensified antiplatelet regimens in obese DM patients remains to be established.

We can conclude that women with T2DM and women without T2DM are underdiagnosed and undertreated.

Lifestyle for prevention of CVD in women with T2DM

Women with T2DM are more likely to be assigned a lower risk category of CVD and receive lifestyle counseling as well as less intensive CVD therapy compared to men. [39] However, DM is a major cardiovascular risk factor in women. With T2DM women have an increased

inflammatory state and greater endothelial dysfunction even at a young age and before menopause. American and European Guidelines advocate lifestyle changes as a first measure for the prevention and management of DM. [15, 39, 40] Specifically, nutrition and physical activity are fundamental in the fight against obesity. Even modest weight loss delays progression from pre-diabetes to T2DM. [41,42] A recent meta-analysis of 63 studies (n=17 272, mean age 49.7 years) showed that each additional kilogram loss was associated with 43% lower odds of T2DM. [42] A diet rich in whole grains, vegetables and yogurt has been shown to reduce the incidence of DM. [43,44,45] In contrast, sugary drinks and red meat are associated with a significant increase in the risk of DM [46,47] However, more than a single food, the diet as a whole and the synergy between the different foods eaten at a meal can better influence health outcomes in a population. [48]

It is not easy for women to adhere to a healthy lifestyle because nowadays they have multiple social roles that require time and energy. [20] In addition, adherence to healthy lifestyle is strongly influenced by socio-economic level, social role, and education. [5,21] This leads to an increase in psychosocial stressors (e.g. anxiety, depression and stress), which are known cardiovascular risk factors. [5,49,50]

Psychosocial factors, like depressive and anxiety disorders and increased child care, familial and home care responsibility, have been shown to increase risk for CVD events in women more so than in men. [49]

The recent COVID-19 pandemic strongly affected women due to increased psychological distress and to the shift to unhealthy lifestyle including diet and physical activity. [50,51,52,53]

The CORONAvirus-SARS-CoV-2 and Diabetes Outcomes (CORONADO) study confirm the close relationship between obesity and COVID-19 severity in patients with T2DM and specifically identified BMI as an independent predictor of poor early prognosis in patients with diabetes hospitalized for COVID-19. [54]

There are also several suggested measures for patients with T2DM and COVID-19 infection. It is primarily recommended to monitor blood glucose frequently and maintain a personalized healthy diet to achieve good glycemic control. [55]

Unhealthy diet contributes to excess energy intakes and weight gain, increasing the risk of developing obesity and in premenopausal women mainly central obesity. [48]

The strong association between diabetes and obesity lead to a new term “Diabesity” used to describe the combined adverse health effects. [56] Diabesity has been defined as the new pandemic. The key components of diabetes-related metabolic dysfunction are adiposity (especially abdominal adiposity), dietary glycemic load, sedentary lifestyle, and psychosocial stress, which promote oxidative stress and chronic inflammation [56].

Sex differences in adipose tissue distribution is characterized by a predominance of subcutaneous tissue in women, which is better adapted for large and long-term storage [8]. The rise in obesity is a key contributor to the burgeoning epidemic of type 2 diabetes mellitus in women.

Healthy Diet and physical activity help women with T2DM in the fight against obesity. In fact, physical activity delays the conversion of pre-diabetes to diabetes and improves glycemic control as well as helping in weight control. [57,58] In addition, regular physical activity prevents CV disease. [58]

Physical activity has several positive effects: it improves heart function, improves metabolic controls, reduces inflammation, and in addition, it reduces stress, improves mood and promotes long-term mental health. Sex also influences the utilization of carbohydrates and lipids as fuel sources. Metabolic adaptation during exercise also differs between the sexes since women preferentially oxidize lipids while men use carbohydrates as the predominant fuel source. Adequate physical activity and a healthy diet improve the immune response. [12,58] After the pandemic, global action in support of a healthy diet and physical activity will be mandatory to encourage people to return to a good lifestyle, although some

irreversible damage has been done. This will be reflected in the future with an increase in cardiovascular disease and diabetes.

Approximately 12% of U.S. adults have diabetes, 90% to 95% of whom have T2DM, with significant heterogeneity according to age, sex, race/ethnicity, and socioeconomic status. Moreover, more than one-third of U.S. adults have prediabetes and are at risk of developing T2DM. An aggressive and comprehensive approach to CV risk factor treatment in adults, both men and women, with T2DM reduces CVD. [59,60]

Therapy with SGLT2i in women.

As the 2019 guidelines developed by the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD) show, therapy for T2DM has undergone important changes. [15] The introduction of new drugs in the guidelines has shifted the focus from DM management to the management of CV risk related diabetes. The therapy is tailored to the patient. It has in fact been seen that even in the presence of a class effect, the individual molecules have different effects and therefore specific therapeutic indications.

Over the past two decades, the presence of women in CV risk clinical trials has consistently remained below 50%. In the last decade, the presence of women in studies on CV disease averaged 33 to 38%. [59,60] To improve enrollment and reduce this gap in clinical trials, it is necessary to promote information among health professionals. In fact, studies on cardiovascular disease published by a female first or senior author, showed a higher enrollment of women. [61] Cultural competence is also a key factor in enrollment: adequate training increases the recruitment of minorities into clinical trials. [62]

Some of the new hypoglycemic drugs introduced in therapy (GLP-1RAs, and SGLT-2 Inhibitors) have shown efficacy in reducing cardiovascular events. [63] Among these drugs, a significant reduction in CV events was reported for the SGLT-2 inhibitors (SGLT-2i).

Clinical data illustrated the promising effects of SGLT-2i on weight, blood pressure, uric acid control and lipid profiles. Four SGLT-2i have been approved for treating DM so far, including empagliflozin, dapagliflozin, and canagliflozin. [63]

The CV effects of long-established oral glucose-lowering drugs i.e. metformin, insulin and Sulfonylureas have not been evaluated in large RCTs, as has been done with more recent drugs. [15] However, observational and registry studies provide supporting evidence that long-term use of metformin improves CV prognosis. [64,65]

ESC-EASD guidelines suggest that in individuals with T2DM and either high risk for cardiovascular disease or established cardiovascular disease, GLP-1RA or SGLT-2is are recommended. However there are no recommendations based on gender.

A recent meta-analysis by Mishriky and colleagues suggested that GLP-1RAs significantly reduce the incidence of MACE in women with type 2 diabetes who have established cardiovascular disease or who have an increased cardiovascular risk, and that SGLT-2is may have comparable effects. [66]

The review concluded that women with T2DM, who are at increased risk for cardiovascular disease, should be considered as potential candidates for SGLT-2i treatment. [66]

A pooled analysis of the EMPA-REG OUTCOME study [67], the CANVAS program [68], the DECLARE-TIMI study [69] and the CREDENCE study [70] performed by Rådholm and colleagues demonstrated there were fewer women than men in all four trials [71]. Specifically, women in the CANVAS program were 35.8%, in the CREDENCE study 33.9%, in the EMPA-REG OUTCOME study 28.8% and in the DECLARE-TIMI 58 study 37.4%. (Table 1)

In the total population the 4 clinical studies reported 3994 MACE events affecting 10.3% of subjects. MACE events were slightly lower in women (9.0%) than in men (11.0%), with a risk ratio for MACE of 0.86 (95% confidence interval (CI) 0.76 to 0.97) for women and 0.88 (95%CI 0.82 to 0.95) for men (p for interaction 0.73) suggesting that the use of the SGLT2i produced similar effects for women and men for all CV endpoints. Furthermore, since the CV risk level for women and men was very similar, SGLT2i therapy resulted in equally broad therapy benefits for both women and men.[71] For the safety outcomes studied in the 4 trials Authors reported no evidence of sex differences.

Zinman et al. reported a secondary pre-specified analysis of the EMPA-REG OUTCOME® trial, that included 28.5% of women, to determine the relative effects of empagliflozin in women vs men. [72] As shown in Table 2 CV death, HF hospitalization and incident or worsening nephropathy rate reductions were not different between women and men. [72] In addition, Authors suggested that hospitalisation for HF, that occurred numerically more frequently than in men, could be related both to underlying factors specific to women or because evidence-based HF therapies are used less often by women. [72]

Li and coworkers examined fourteen small trials enrolling 3,157,259 patients in order to analyze real world data. They found that the percentage of women ranged from 35% to 47.7% confirming that the enrollment of women in clinical trials is lower than that of men. [73]

Future development.

Diabetes is a major cardiovascular risk factor in women. Women With T2DM show an increased inflammatory state and greater endothelial dysfunction even at a young age and before menopause. Specific clinical trials need to be conducted to evaluate the efficacy of both preventive and therapeutic interventions in women with T2DM. Furthermore, studies are

needed to evaluate the effect of the new hypoglycemic drugs, which have already demonstrated a reduction effect in cardiovascular events, when they are dedicated to the specific evaluation of women with T2DM.

Acknowledgements

We would like to thank Mrs Janet Ann Carter for editing the paper.

References

1. American Heart Association. Cardiovascular disease & diabetes. 2015 http://www.heart.org/HEARTORG/Conditions/More/Diabetes/WhyDiabetesMatter Cardiovascular-Disease-Diabetes_UCM_313865_Article. jsp/#.Wh_-eNKg_RY. Accessed 11 Feb 2021
2. Cho NH, Shaw JE, Karuranga S et al. IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract* 138:271–281 (2018). https://doi.org/10.1016/j.diabres.2018.02.023
3. NCD Risk Factor Collaboration (NCD-RisC) Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet* 387 (10027):1513–1530 (2016). https://doi.org/10.1016/S0140-6736(16) 00618-
4. Peters SA, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events. *Diabetologia*. 57:1542–51 (2014).
5. Mattioli AV, Sciomer S, Moscucci F et al. Cardiovascular prevention in women: a narrative review from the Italian Society of Cardiology working groups on 'Cardiovascular Prevention, Hypertension and peripheral circulation' and on 'Women Disease'. *J Cardiovasc Med* 20:575-583 (2019). doi:10.2459/JCM.0000000000000831
   •• A comprehensive review on risk factors with a focus on women.
6. D'Ascenzi F, Sciaccaluga C, Cameli M, et al. When should cardiovascular prevention begin? The importance of antenatal, perinatal and primordial prevention. Eur J Prev Cardiol. 2019 Dec 16:2047487319893832. doi: 10.1177/2047487319893832. Epub ahead of print. PMID: 31838885.

7. Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. *Lancet* 383(9933):1973-80. (2014) doi: 10.1016/S0140-6736(14)60040-4.
8. Goossens GH, Jocken JWE, Blaak EE. Sexual dimorphism in cardiometabolic health: the role of adipose tissue, muscle and liver. *Nat Rev Endocrinol* 17(1):47-66. (2021) doi: 10.1038/s41574-020-00431-8. Epub 2020 Nov 10. PMID: 33173188. Diventa 5
9. Strain WD, Paldánius PM. Diabetes, cardiovascular disease and the microcirculation. *Cardiovasc Diabetol*. Apr 18;17(1):57 (2018). doi: 10.1186/s12933-018-0703-2. PMID: 29669543; PMCID: PMC5905152
10. Brohall G, Odén A, Fagerberg B. Carotid artery intima-media thickness in patients with type 2 diabetes mellitus and impaired glucose tolerance: a systematic review. *Diabet Med* 23:609–16 (2006)
11. Rizzoni D, Porteri E, Guelfi D, et al. Structural alterations in subcutaneous small arteries of normotensive and hypertensive patients with non-insulin-dependent diabetes mellitus. *Circulation*.;103:1238–44 (2001)
12. Balla S, Gomez SE, Rodriguez F. Disparities in Cardiovascular Care and Outcomes for Women From Racial/Ethnic Minority Backgrounds. *Curr Treat Options Cardiovasc Med* 22(12):75. (2020) doi: 10.1007/s11936-020-00869-z.
13. Mattioli AV, Pinti M, Farinetti A, Nasi M. Obesity risk during collective quarantine for the COVID-19 epidemic. *Obesity Medicine* Dec; 20: 100263 (2020). doi: 10.1016/j.obmed.2020.100263.
14. Maggio CA, Pi-Sunyer FX. Obesity and type 2 diabetes. *Endocrinol Metab Clin North Am*. Dec;32(4):805-22 (2003) doi: 10.1016/s0889-8529(03)00071-9. PMID: 14711063.]
15. Cosentino F, Grant PJ, Aboyans V, et ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in

collaboration with the EASD. *Eur Heart J*. 7;41(2):255-323 (2020). doi: 10.1093/eurheartj/ehz486. PMID: 31497854

16. Valensi P, Lorgis L, Cottin Y. Prevalence, incidence, predictive factors and prognosis of silent myocardial infarction: a review of the literature. *Arch Cardiovasc Dis* 104:178-188 (2011)
17. Henning RJ. Type-2 diabetes mellitus and cardiovascular disease. *Future Cardiol*. Nov;14(6):491-509. (2018) doi: 10.2217/fca-2018-0045.
    •• A comprehensive review on diabetes and cardiovascular disease.
18. Maffei S, Cugusi L, Meloni A et al Working Group of Gender Cardiovascular Disease of the Italian Society of Cardiology (SIC), Italian Society of Obstetrics, Gynecology (SIGO). IGENDA protocol: gender differences in awareness, knowledge and perception of cardiovascular risk: an Italian multicenter study. *J Cardiovasc Med*. 20(5):278-283 (2019). doi: 10.2459/JCM.0000000000000761.
19. Hammond J, Salamonson Y, Davidson P, et al. Why do women underestimate the risk of cardiac disease? A literature review. *Aust Crit Care* 20:53–59 (2007).
20. Kusnoor AV, Ferguson AD, Falik R. Ischemic heart disease in women: a review for primary care physicians. *South Med J* 104: 200–204 (2011).
21. Sciomer S, Moscucci F, Maffei S, Gallina S, Mattioli AV. Prevention of cardiovascular risk factors in women: The lifestyle paradox and stereotypes we need to defeat. *Eur J Prev Cardiol*. 26(6):609-610 (2019). doi: 10.1177/2047487318810560
22. Woodward M. Cardiovascular disease and the female disadvantage. *Int J Environ Res Public Health*;16:1165 (2019).
23. Maffei S, Guiducci L, Cugusi L, et al Working Group on "Gender difference in cardiovascular disease" of the Italian Society of Cardiology. Women-specific predictors of cardiovascular disease risk - new paradigms. *Int J Cardiol*.;286:190-197. (2019)

doi: 10.1016/j.ijcard.2019.02.005.

24. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet* 373:1773–9. (2009)

• A metaanalysis on gestational diabetes

25. Carr DB, Utzschneider KM, Hull RL, et al. Gestational diabetes mellitus increases the risk of cardiovascular disease in women with a family history of type 2 diabetes. *Diabetes Care* 29:2078–83 (2006).

26. Humphries KH, Izadnegahdar M, Sedlak T, et al. Sex differences in cardiovascular disease - Impact on care and outcomes. *Front Neuroendocrinol.* Jul;46:46-70 (2017). doi: 10.1016/j.yfrne.2017.04.001.

27. Lee CMY, Mnatzaganian G, Woodward M, et al. Sex disparities in the management of coronary heart disease in general practices in Australia. *Heart* 105:1898-1904 (2019)

28. Turnbull F, Arima H, Heeley E, et al. Gender disparities in the assessment and management of cardiovascular risk in primary care: the AusHEART study. *Eur J Cardiovasc Prev Rehabil* 18:498–503 (2011).

29. Manteuffel M, Williams S, Chen W, et al. Influence of patient sex and gender on medication use, adherence, and prescribing alignment with guidelines. *J Womens Health* 23:112–9 (2014).

30. Abuful A, Gidron Y, Henkin Y. Physicians' attitudes toward preventive therapy for coronary artery disease: is there a gender bias? *Clin Cardiol* 28:389–393 (2005).

31. Stone NJ, Robinson JG, Lichtenstein AH, et al., American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of

Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 129 (25 Suppl 2):S1– S45 (2014).

32. Zhang H, Plutzky J, Shubina M, Turchin A. Drivers of the Sex Disparity in Statin Therapy in Patients with Coronary Artery Disease: A Cohort Study. *PLoS ONE* 11(5): e0155228 (2016). doi:10.1371/journal.pone.0155228
33. Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. *JAMA*;295:306-313. (2006)
34. Mattioli AV, Manenti A, Farinetti A. Sex differences in adherence to guidelines in aspirin prescription in a population of low-risk cardiovascular patients. Eur J Prev Cardiol. 2018 Apr;25(6):606-607. doi: 10.1177/2047487318758433. Epub 2018 Feb 7.
35. Gaziano JM, Brotons C, Coppolecchia Ret al; ARRIVE Executive Committee. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. *Lancet*;392:1036-1046. (2018)
36. ASCEND Study Collaborative Group, Bowman L, Mafham M, Wallendszus K, et al. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med* 379: 1529-1539 (2018)
37. Rothwell PM, Cook NR, Gaziano JM, et al. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials. *Lancet* 392:387-399. (2018)
38. Rocca B, Fox KAA, Ajjan RA, et al. Antithrombotic therapy and body mass: an expert position paper of the ESC Working Group on Thrombosis. *Eur Heart J* 39:1672-1686 (2018)
39. American Diabetes Association. 4. Lifestyle management: Standards of Medical Care in Diabetes-2018. *Diabetes Care* 41:S38-S50 (2018)

40. Evert AB, Boucher JL, Cypress M, et al. Nutrition therapy recommendations for the management of adults with diabetes. *Diabetes Care* 37:S120S143 (2014).
41. Balk EM, Earley A, Raman G, Avendano EA, Pittas AG, Remington PL. Combined diet and physical activity promotion programs to prevent type 2 diabetes among persons at increased risk: a systematic review for the Community Preventive Services Task Force. *Ann Intern Med* 163:437-451 (2015)
42. Galaviz KI, Weber MB, Straus A, Haw JS, Narayan KMV, Ali MK. Global diabetes prevention interventions: a systematic review and network meta-analysis of the real-world impact on incidence, weight, and glucose. *Diabetes Care* 41:1526-1534 (2018)
43. Aune D, Norat T, Romundstad P, Vatten LJ. Whole grain and refined grain consumption and the risk of type 2 diabetes: a systematic review and dose–response meta-analysis of cohort studies. *Eur J Epidemiol* 28(11):845–858 (2013). doi: 10.1007/s10654-013-9852-5.
44. Carter P, Gray LJ, Troughton J, Khunti K, Davies MJ. Fruit and vegetable intake and incidence of type 2 diabetes mellitus: systematic review and meta-analysis. *BMJ*. 341:c4229 (2010).
45. Mattioli AV, Coppi F, Migaldi M, Farinetti A. Fruit and vegetables in hypertensive women with asymptomatic peripheral arterial disease. *Clinical Nutrition ESPEN* 27, 110–112 (2018).
46. Imamura F, O'Connor L, Ye Z, et al. Consumption of sugar sweetened beverages, artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: systematic review, meta-analysis, and estimation of population attributable fraction. *BMJ*.351:h3576 (2015).
47. Pan A, Sun Q, Bernstein AM, et al. Red meat consumption and risk of type 2 diabetes: 3 cohorts of US adults and an updated meta-analysis. *Am J Clin Nutr* 94(4):1088–1096 (2011) .doi: 10.3945/ajcn.111.018978.

48. Allaire BT, Tjaden AH, Venditti EM, et DPP Research Group. Diet quality, weight loss, and diabetes incidence in the Diabetes Prevention Program (DPP). *BMC Nutr*. Dec 15;6(1):74 (2020). doi: 10.1186/s40795-020-00400-4.

49. Low CA, Thurston RC, Matthews KA. Psychosocial factors in the development of heart disease in women: current research and future directions. *Psychosom Med*. 72:842–54 (2010).

50. Mattioli AV, Nasi M, Cocchi C, Farinetti A. COVID 19 outbreak: impact of the quarantine-induced stress on cardiovascular disease risk burden. *Future Cardiology* 16(6), pp. 539–542 (2020). doi: 10.2217/fca-2020-0055.

•• A comprehensive review on effects of quarantine on cardiovascular risk.

51. Brooks SK, Webster RK, Smith LE, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence *Lancet*; 395: 912–20 (2020). https://doi.org/10.1016/ S0140-6736(20)30460-8

52. Louvardi M, Pelekasis P, Chrousos G, Darviri C. Mental Health in Chronic Disease Patients during the COVID-19 Quarantine in Greece. *Palliative and Supportive Care* 1-17 (2020) doi:10.1017/S1478951520000528

53. Mattioli, A.V., Sciomer, S., Maffei, S., Gallina, S. Lifestyle and Stress Management in Women During COVID-19 Pandemic: Impact on Cardiovascular Risk Burden. *Am J Lifestyle Med* in press (2020) doi: 10.1177/1559827620981014

54. Smati S, Tramunt B, Wargny M, for the CORONADO investigators. Relationship between obesity and severe COVID-19 outcomes in patients with type 2 diabetes: Results from the CORONADO study. *Diabetes Obes Metab*. Feb;23(2):391-403. (2021) doi: 10.1111/dom.14228.

55. Baidya A, Singh SK, Bajaj S, et al. Diabetes and COVID-19: A Review. *J ASEAN Fed Endocr Soc* 35(1):40-48 (2020). doi: 10.15605/jafes.035.01.06.

56. Wells JCK. The diabesity epidemic in the light of evolution: insights from the capacity-load model. *Diabetologia*. Oct;62(10):1740-1750.(2019) doi: 10.1007/s00125-019-4944-8.
57. Sluik D, Buijsse B, Muckelbauer R, et al. Physical activity and mortality in individuals with diabetes mellitus: a prospective study and meta-analysis. *Arch Intern Med* 172:1285-1295 (2012).
58. Nasi M, Patrizi G, Pizzi C, et al. The role of physical activity in individuals with cardiovascular risk factors: an opinion paper from Italian Society of Cardiology-Emilia Romagna-Marche and SIC-Sport. *J Cardiovasc Med* Oct;20(10):631-639 (2019). doi: 10.2459/JCM.0000000000000855.
59. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019 Sep 10;140(11):e596-e646. doi: 10.1161/CIR.0000000000000678. Epub 2019 Mar 17].
60. Cho L, Davis M, Elgendy I, Epps K, Lindley KJ, Mehta PK, Michos ED, Minissian M, Pepine C, Vaccarino V, Volgman AS; ACC CVD Womens Committee Members. Summary of Updated Recommendations for Primary Prevention of Cardiovascular Disease in Women: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020 May 26;75(20):2602-2618. doi: 10.1016/j.jacc.2020.03.060. PMID: 32439010.
61. Jin X, Chandramouli C, Allocco B, Gong E, Lam CSP, Yan LL. Women's participation in cardiovascular clinical trials from 2010 to 2017. *Circulation* 141:540–8 (2020).
• A n important update.
62. Gong IY, Tan NS, Ali SH, et al. Temporal trends of women enrollment in major cardiovascular randomized clinical trials. *Can J Cardiol* 35:653–60 (2019).

63. Reza N, Tahhan AS, Mahmud N, et al. Representation of women authors in international heart failure guidelines and contemporary clinical trials. *Circ Heart Fail* 13:e006605 (2020)
64. Wells JS, Pugh S, Boparai K, Rearden J, Yeager KA, Bruner DW. Cultural competency training to increase minority enrollment into radiation therapy clinical trials-an NRG oncology RTOG study. *J Cancer Educ* 32:721–7 (2017).
65. Pan X, Xu S, Li J, Tong N. The Effects of DPP-4 Inhibitors, GLP-1RAs, and SGLT-2/1 Inhibitors on Heart Failure Outcomes in Diabetic Patients With and Without Heart Failure History: Insights From CVOTs and Drug Mechanism. *Front Endocrinol Dec* 1;11:599355 (2020). doi: 10.3389/fendo.2020.599355.
66. Maruthur NM, Tseng E, Hutfless S, et al.Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med*;164:740-751 (2016).
67. Scheen AJ, Paquot N. Metformin revisited: a critical review of the benefit-risk balance in at-risk patients with type 2 diabetes. *Diabetes Metab* 39:179-190 (2013).
68. Mishriky BM, Okunrintemi V, Jain S, Sewell KA, Powell JR, Cummings DM. Do GLP-1RAs and SGLT-2is reduce cardiovascular events in women with type 2 diabetes? A systematic review and meta-analysis. *Diabetes Metab*. May 18:S1262-3636(20)30076-8.(2020). doi: 10.1016/j.diabet.2020.05.002
•• A review and analysis of recent clinical trial exploring the effects on women
69. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med.* 373(22): 2117-28. (2015)
70. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med* 377(7):644-57 (2017)
71. Norhammar A, Bodegård J, Nyström T, Thuresson M, Nathanson D, Eriksson JW. Dapagliflozin and cardiovascular mortality and disease outcomes in a population with

type 2 diabetes similar to that of the DECLARE-TIMI 58 trial: A nationwide observational study. *Diabetes Obes Metab* May;21(5):1136-1145. (2019) doi: 10.1111/dom.13627. Epub 2019 Feb 6. PMID: 30609272; PMCID: PMC6593417.

72. Perkovic V, Jardine MJ, Neal B, et al CREDENCE Trial Investigators. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med*. Jun 13;380(24):2295-2306. (2019) doi: 10.1056/NEJMoa1811744. Epub 2019 Apr 14. PMID: 30990260.
73. Rådholm K, Zhou Z, Clemens K, Neal B, Woodward M. Effects of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes in women versus men. *Diabetes Obes Metab* 22(2):263-266 (2020). doi: 10.1111/dom.13876.
74. Zinman B, Inzucchi SE, Wanner C, et EMPA-REG OUTCOME® investigators. Empagliflozin in women with type 2 diabetes and cardiovascular disease - an analysis of EMPA-REG OUTCOME®. *Diabetologia* 61(7):1522-1527 (2018). doi: 10.1007/s00125-018-4630-2.
75. Li CX, Liang S, Gao L, Liu H. Cardiovascular outcomes associated with SGLT-2 inhibitors versus other glucose-lowering drugs in patients with type 2 diabetes: A real-world systematic review and meta-analysis. *PLoS One*. Feb 19;16(2): (2021) e0244689. doi: 10.1371/journal.pone.0244689. PMID: 33606705

Table legend:

Table 1

Cardiovascular outcome in 4 RCT trials in total population and in women.

Table 2

Comparison of outcome in men and women in the EMPA-REG Outcome Study [70]