Review

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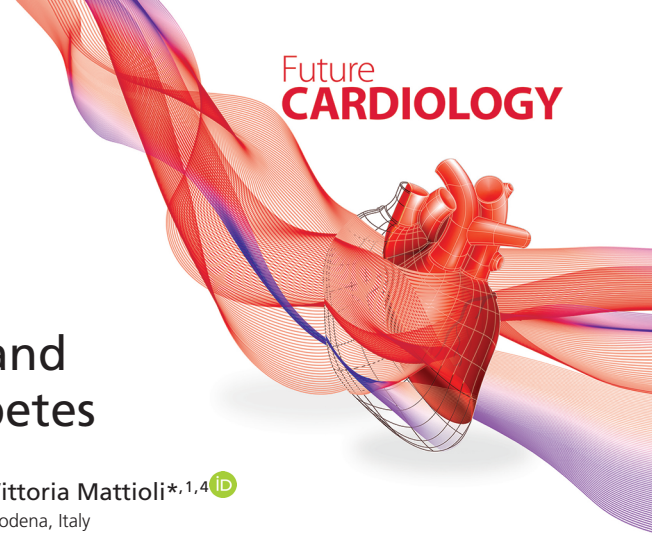

Cardiovascular disease prevention and therapy in women with Type 2 diabetes

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Cardiovascular disease (CVD) is the leading cause of death among men and women, although women are usually underdiagnosed and experience a delay in diagnosis. This also occurs in women with type 2 diabetes mellitus, despite the fact that diabetes is recognized as a major cardiovascular risk factor. Several factors influence the gap between diagnosis and treatment of cardiovascular disease in women: lack of perception of cardiovascular risk, effects of sex-related risk factors and the action of drugs in women. Women with Type 2 diabetes mellitus are more likely to be assigned a lower CVD risk category and to receive lifestyle counseling as well as less intensive CVD therapy compared with men. The present narrative review aims to analyze the risk of CVD in women with Type 2 diabetes mellitus and whether there is a difference between men and women in the efficacy of SGLT-2 inhibitors, new hypoglycemic drugs.

Lay abstract: Despite the fact that cardiovascular disease is the most frequent cause of death in women in industrialized countries, the idea that it affects mainly men and affects women only after menopause still persists. This results in underdiagnosis and undertreatment of cardiovascular disease in women. This phenomenon depends on various factors, including lack of perception of risk in women themselves, reduced social action regarding prevention of cardiovascular disease risk factors in women and lower presence of women in the populations included in scientific studies. The condition is also present in women with Type 2 diabetes mellitus, 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 Type 2 diabetes mellitus. Failure to identify risk carries a high social and economic cost.

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According to the American Heart Association statement, at least 68% of people aged 65 or older with diabetes die of some form of cardiovascular disease (CVD), and 16% die of stroke. Adults with diabetes are two- to four-times more likely to die of CVD than adults without diabetes [1].

In the adult population, diabetes is more prevalent in men than women [2]. In addition, the peak in diabetes prevalence occurs earlier in men (65–69 years of age) than 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 women (from 5 to 8%) between 1980 and 2014. The International Diabetes Federation also noted 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) have a greater rate of cardiovascular (CV) death, and the years of life lost because of the disease are higher (6.8, 6.4 and 5.4 years in women vs 6.3, 5.8 and 4.5 years in men, all respectively 40, 50 and 60 years old) [5]. The risk of major CV events in women with T2DM is present 20–30 years earlier than in women without T2DM, mitigating the premenopausal 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 because of 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 CVD, women are underdiagnosed and undertreated compared with men; due to the link between diabetes and CVD, we aim to find out if women with T2DM were equally underestimated compared with men. The authors analyzed the several reasons that underlie the differences in treatment and efficacy of drugs in women with T2DM.

CVD in women with T2DM

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

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

Another reason is related to the different CVD risk profile in women with T2DM. Women with T2DM are less likely to achieve target values for systolic blood pressure, low-density lipoprotein and high-density lipoprotein cholesterol, fasting plasma glucose and hemoglobin A1c. Regarding treatment, women are more likely than men to take insulin, either alone or in combination with oral hypoglycemic drugs [12]. Although aging induces body composition changes in both sexes, menopause predisposes women to the accumulation of visceral fat. With regard to the impact of female sex on risk factors for 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]. In addition, obesity and T2DM are associated with systemic inflammation, leading to endothelial dysfunction [3,14].

European Society of Cardiology (ESC) guidelines for the diagnosis and management of prediabetes and diabetes emphasize that the addition of circulating biomarkers for CVD risk assessment has limited clinical value. In patients with diabetes without CVD, measurement of inflammatory markers (e.g., C-reactive protein) adds little incremental value to risk assessment [15]. Furthermore, the differences between women and men have not yet been systematically explored. The diagnostic approach to CVD is similar in women and men with T2DM. However, several studies have reported some differences between the sexes [15,16]. For example, a resting ECG may detect silent myocardial infarction in 4% of individuals with diabetes, but this is associated with an increased risk of CVD and all-cause mortality in men only. As suggested by ESC guidelines, sex-specific differences in the diagnosis of CVD require further investigation.

Women of all ages have a lower risk of sudden cardiac death compared with men, but in the presence of diabetes, the risk of sudden cardiac death is quadrupled in both men and women [15]. Moreover, although CVD remains the leading cause of death among men and women, women are usually underdiagnosed and may have a delay in diagnosis [5]. The gap between the diagnosis and treatment of CVD in women depends on several factors: lack of perception of CVD risk, which leads to a delay in diagnosis; exposure to risk factors that act differently in women and men as well as specific sex-related risk factors that are still little known; and possible difference in drug action in women. Despite the broad consensus that diabetes is a major CVD risk factor, this gap also occurs in women with T2DM [5,17].

Lack of perception of CVD risk

In recent years, physicians' awareness of CVD risk in women has increased, reducing underdiagnosis 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 frequency of CVD. There are several reasons for this: lack of CVD research specifically dedicated to women, insufficient education specifically aimed at women with regard to female-specific CVD risk factors and underestimation by the national health system of the prevalence of CVD among women [19–21]. 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].

Differences in effects of risk factor exposure in women & men & sex-specific risk factors

The exact reasons for observed sex differences in risk factors are not known and depend on many biological and sociocultural contributors. Hypertension is highly prevalent among women – in particular, non-Hispanic black women – compared with other groups. Higher BMI and waist circumference likely contribute to higher blood pressure, cholesterol levels and diabetes prevalence in men. Diabetes is also a strong risk factor for CVD and heart failure among women. Sex differences in CVD risk cannot be explained by only estrogen or progesterone levels. The risk of death from CVD in men is higher than that seen in women throughout the life span, without the rapid rise in the age–CVD mortality curve in women, rise occurring at the time of menopause, despite large differences in endogenous estradiol and progesterone levels before and after menopause, and postmenopausal exogenous estrogen does not appear to influence the risk of CVD [5,23]. Furthermore, sex hormones such as estrogen and testosterone are likely to contribute to sex differences in blood pressure and CVD.

Recently, researchers have studied CVD risk factors that are unique to women and related to their reproductive history. 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 (e.g., 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 CVD: gestational diabetes, gestational hypertension and preeclampsia, intrauterine growth restriction and preterm birth [5,23,24]. All of these conditions, which develop during the fertile period of life or perimenopause, may affect the onset, clinical features and prognosis of CVD later in women's lives and have recently been suggested to be early markers of future CVD. Therefore, CVD risk stratification in women should also include an assessment of these specific risk factors.

Women who develop gestational diabetes have a higher risk of developing CV events and T2DM over their life span [24,25]. A meta-analysis of 675,455 women confirmed that women with gestational diabetes have a significantly higher risk of developing subsequent T2DM (risk ratio = 7.43; 95% CI: 4.79–11.51). In addition, women with a family history of T2DM who have developed gestational diabetes are more likely to have CVD risk factors – specifically, metabolic syndrome – and to experience CV events at a young age. In this group of women, the relative risk is 4.69 within the first 5 years postpartum and 9.34 beyond 5 years postpartum. Therefore, gestational diabetes could be an early biomarker of CVD that is indicative of a high-risk category of women and suitable for early prevention [5,24]. However, the degree to which an increased CVD risk associated with female-specific conditions occurs independent of conventional CVD risk factors is unknown [15].

Different actions of drugs used in CVD prevention

There are sex-related differences in CV medications. Men with T2DM or CVD are diagnosed earlier and are more often treated with aspirin, statins and antihypertensive treatments compared with women and are therefore more likely to achieve recommended treatment targets for risk factors [26–29]. 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 (e.g., body dimension and composition, metabolism, gastric and hepatic differences, renal functions) could influence the activity of many drugs, including their bioactive compounds and interactions with other drugs, foods and beverages [28]. Women are less represented in randomized controlled trials (relative to their overall representation in disease populations), and adherence to therapy is consistently lower in women with T2DM compared with men. It is important to consider sex differences in treatment modalities and drug metabolism (i.e., sex-specific cytochrome expression). Moreover, even when drugs are prescribed, treatment is often less aggressive and does not achieve optimal goals (e.g., women with T2DM have higher levels of glycated hemoglobin). A major issue is that postmenopausal women are less likely to be treated with statins and aspirin than men with a similar CVD risk [29].

Several reasons have been put forward to explain this gap (e.g., a limitation on the prescription of statins in women seems to be the greater tendency to develop myopathies) [30]. To reduce this gap, American Heart

Association/American College of Cardiology primary prevention guidelines for statin initiation include 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 received statins, and less than 70% maintain adherence to therapy over time [32]. The researchers reported that four 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. However, these suboptimal treatment patterns lead to higher mortality and poorer CVD outcomes compared with 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]. However, 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) trial evaluated 15,480 patients with diabetes without CVD treated with 100 mg aspirin once daily or placebo. The researchers found a significant difference in the primary composite efficacy outcome (myocardial infarction, stroke, transient ischemic attack or death from any cause), which occurred in 658 (8.5%) patients treated with aspirin versus 743 (9.6%) treated with placebo (risk ratio = 0.88; 95% CI: 0.79–0.97; p = 0.01) [36].

It has recently been suggested that body weight or size may 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 diabetic patients remains to be established. On the basis of these observations, we can affirm 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 with men [39]. However, diabetes is a major CVD 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 diabetes [15,39,40]. Specifically, nutrition and physical activity are fundamental in the fight against obesity. Even modest weight loss delays progression from prediabetes to T2DM [41,42]. A recent meta-analysis of 63 studies (n = 17,272; mean age: 49.7 years) showed that each additional kilogram lost was associated with 43% lower odds of developing T2DM [42]. A diet rich in whole grains, vegetables and yogurt has been shown to reduce the incidence of diabetes [43–45]. By contrast, sugary drinks and red meat are associated with a significant increase in the risk of diabetes [46,47]. However, beyond just 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 they currently have multiple social roles that require time and energy [20]. In addition, adherence to a healthy lifestyle is strongly influenced by socioeconomic level, social role and education [5,21]. This leads to an increase in psychosocial stressors (e.g., anxiety, depression and stress), which are known CVD risk factors [5,49,50].

Psychosocial factors, such as depressive and anxiety disorders and increased child care, familial and home care responsibilities, have been shown to increase the risk of CVD events in women more so than in men [49]. The recent coronavirus disease 2019 (COVID-19) pandemic has strongly affected women as a result of increased psychological distress and the shift to an unhealthy lifestyle, including diet and physical activity [50–53]. The CORONADO study confirmed 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 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]. An unhealthy diet contributes to excess energy intake and weight gain, increasing the risk of obesity and, in premenopausal women, central obesity [48].

The strong association between diabetes and obesity has led to a new term, "diabesity," which is used to describe their 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.

Sex differences in adipose tissue distribution are characterized by a predominance of subcutaneous tissue in women, which is better adapted for greater and longer-term storage [8]. The rise in obesity is a key contributor to the burgeoning epidemic of T2DM in women. A healthy diet and physical activity help women with T2DM in the fight against obesity. In fact, physical activity delays the conversion of prediabetes to diabetes, improves glycemic control and aids in weight control [57,58]. In addition, regular physical activity prevents CVD [58].

Physical activity has several positive effects: it improves heart function and metabolic control, reduces inflammation and 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, with women preferentially oxidizing lipids and men using carbohydrates as the predominant fuel source.

In addition, 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. However, some irreversible damage has been done and will be reflected in the future by an increase in CVD and diabetes.

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

Therapy with SGLT-2 inhibitors in women

As the 2019 guidelines developed by the ESC and the European Association for the Study of Diabetes show, therapy for T2DM has undergone important changes [15]. The introduction of new drugs in the guidelines has shifted the focus from diabetes management to the management of CVD risk-related diabetes. The therapy is tailored to the patient, as 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 CVD risk clinical trials has consistently remained below 50%. In the last decade, the presence of women in studies on CVD averaged 33–38% [61,62]. To improve enrollment and reduce this gap in clinical trials, it is necessary to promote information among health professionals. In fact, studies on CVD published by a female first or senior author show a higher enrollment of women [63]. Cultural competence is also a key factor in enrollment, as adequate training increases the recruitment of minorities into clinical trials [64].

Some of the new hypoglycemic drugs introduced in therapy (GLP-1 receptor agonists and SGLT-2 inhibitors [SGLT-2is]) have shown efficacy in reducing CV events [65]. Among these drugs, a significant reduction in CV events has been reported with SGLT-2is. Clinical data have illustrated the promising effects of SGLT-2is on weight, blood pressure, uric acid control and lipid profiles. Four SGLT-2is have been approved thus far for the treatment of diabetes, including empagliflozin, dapagliflozin and canagliflozin [65].

The CV effects of long-established oral glucose-lowering drugs (i.e., metformin, insulin and sulfonylureas) have not been evaluated in large randomized controlled trials, 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 [66,67].

ESC–European Association for the Study of Diabetes guidelines suggest that in individuals with T2DM and either high risk of CVD or established CVD, GLP-1 receptor agonists or SGLT-2is are recommended. However, there are no recommendations based on sex. A recent meta-analysis by Mishriky *et al.* suggested that GLP-1 receptor agonists significantly reduce the incidence of major adverse CV events (MACE) in women with T2DM who have established CVD or an increased CVD risk and that SGLT-2is may have comparable effects [68]. The review concluded that women with T2DM, who are at increased risk of CVD, should be considered potential candidates for SGLT-2i treatment.

A pooled analysis of the EMPA-REG OUTCOME study [69], CANVAS program [70], DECLARE-TIMI 58 study [71] and CREDENCE study [72] performed by Rådholm *et al.* demonstrated that there were fewer women than men in all four trials [73]. Specifically, women comprised 35.8% of participants in the CANVAS program, 33.9% of participants in the CREDENCE study, 28.8% of participants in the EMPA-REG OUTCOME study and 37.4% of participants in the DECLARE-TIMI 58 study (Table 1).

In the total population, the four clinical studies reported 3994 MACE events affecting 10.3% of subjects. MACE events were slightly lower in women (9.0%) compared with men (11.0%), with a risk ratio for MACE of 0.86

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Table 1. CV outcome in four RCTs in total population and women.

Study	Participants			CV outcome		Ref.
	Total (n)	Men (n)	Women, n (%)	Population, HR (95% CI)	Women, HR (95% CI)	
EMPA-REG OUTCOME	7020	5016	2004 (28.5)	0.86 (0.74–0,99)	0.83 (0.62–1.11)	[69,74]
CANVAS program	10,142	6509	3633 (35.8)	0.86 (0.75–0,97)	0.84 (0.66–1.06)	[70]
DECLARE-TIMI 58	17,160	10,738	6422 (37.4)	0.79 (0.69–0.92)	–	[71]
CREDENCE	4401	2907	1494 (33.9)	0.70 (0.59–0.82)	0.87 (0.63–1.20)	[72]

CV: Cardiovascular; HR: Hazard ratio; RCTs: Randomized controlled trials.

Table 2. Comparison of outcomes in men and women in the EMPA-REG OUTCOME study.

EMPA-REG OUTCOME endpoint	Men, HR (95% CI)	Women, HR (95% CI)	p-value for treatment by sex interaction
3-point MACE	0.87 (0.73–1.02)	0.83 (0.62–1.11)	0.8114
CV deaths	0.58 (0.45–0.75)	0.76 (0.48–1.20)	0.3219
HF hospitalizations over time	0.73 (0.53–1.01)	0.50 (0.31–0.81)	0.1981
Occurrence of worsening nephropathy	0.61 (0.52–0.71)	0.62 (0.48–0.80)	0.8543

CV: Cardiovascular; HF: Heart failure; HR: Hazard ratio; MACE: Major adverse cardiovascular events.
Data taken from [74].

(95% CI: 0.76–0.97) for women and 0.88 (95% CI: 0.82–0.95) for men (interaction p = 0.73), suggesting that the use of the SGLT-2i produced similar effects in women and men for all CV endpoints. Furthermore, since the CVD risk level for women and men was very similar, SGLT-2i therapy resulted in equally broad therapy benefits for both women and men [73]. With regard to the safety outcomes studied in the four trials, the researchers reported no evidence of sex differences.

Zinman *et al.* reported a secondary prespecified analysis of the EMPA-REG OUTCOME trial, which included 28.5% women, to determine the relative effects of empagliflozin in women versus men [74]. As shown in Table 2, reductions in CV deaths, heart failure hospitalizations and occurrence of worsening nephropathy were not different between women and men. In addition, the researchers suggested that hospitalization for heart failure, which occurred more frequently in women than men, could be related to underlying factors specific to women or to the fact that evidence-based heart failure therapies are used less often by women.

To analyze real-world data, Li *et al.* examined 14 small trials enrolling 3,157,259 patients [75]. The researchers 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.

Future perspective

Diabetes is a major CVD 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 on new oral hypo-glycemic agents specifically dedicated to evaluating the effects on women with T2DM are needed to confirm the data observed on the general population.

Executive summary

Cardiovascular disease in women with Type 2 diabetes mellitus

- Cardiovascular disease (CVD) is the primary cause of death among women with Type 2 diabetes mellitus (T2DM).
- The impact of diabetes on the development of CVD is greater in women.
- Women are usually underdiagnosed and may receive delayed diagnosis of CVD as a result of several factors.

Lifestyle for prevention of CVD in women with T2DM

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

Therapy with SGLT-2 inhibitors in women

- Some of the new hypoglycemic drugs (GLP-1 receptor agonists and SGLT-2 inhibitors) have shown efficacy in reducing cardiovascular events in both women and men.
- The presence of women in CVD risk clinical trials has consistently remained below 50%. Similarly, women are underrepresented in SGLT-2 inhibitor trials.

Author contributions

A V Mattioli and A Farinetti conceived of the idea upon which the article is based. C Cocchi, A V Mattioli, F Coppi and A Farinetti developed the different parts of the manuscript and performed the final supervision. All authors contributed to and approved the final manuscript.

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