- Copyright - Il Pensiero Scientifico Editore downloaded by IP 18.97.14.82 Sat, 05 Sep 2026, 20:04:32

Gender differences in type 2 diabetes (Italy)

Valeria Manicardi[1], Maria Chiara Rossi[2], Elisabetta L Romeo[3], Annalisa Giandalia[3], Mariella Calabrese[4], Elena Cimino[5], Daniela Antenucci[6], Paola Bollati[7], Patrizia Li Volsi[8], Ada Maffettone[9], Guglielmina Speroni[10], Concetta Suraci[11], Elisabetta Torlone[12], Giuseppina Russo[3] (on behalf of Gruppo Donna AMD)

1. Department of Internal Medicine, Hospital of Montecchio, AUSL of Reggio Emilia, Italy; 2. CORESEARCH - Center for Outcomes Research and Epidemiology srl, Pescara, Italy; 3. Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy; 4. Diabetology Department, Prato, Italy; 5. Diabetology, Hospital of Niguarda, Milan, Italy; 6. Endocrinology, Lanciano (Chieti), Italy; 7. Department of Internal Medicine and Diabetology, San Carlo Hospital, Milan, Italy; 8. Diabetology Department, AAS5, Pordenone, Italy; 9. Metabolic Unit, Hospital of Monaldi, Naples, Italy; 10. Department of Internal Medicine and Diabetology, Hospital of Codogno (ASST Lodi), Italy; 11. Diabetology, San Paolo Hospital, Civitavecchia (Rome), Italy; 12. AO MISEM, Perugia, Italy.
Received 2 March 2016; accepted 11 March 2016.

Summary. The impact of diabetes on cardiovascular risk is particularly evident in women who are most affected by major cardiovascular events, especially myocardial infarction, and have a higher mortality, confirming the loss of protection by estrogens in childbearing age. Italian data from the *AMD Annals* have documented that the achievement of targets for the major CV risk factors is systematically unfavorable to women with diabetes T2: women are more obese, have a worse control of diabetes and especially a worse lipid profile, and a higher frequency of reduction in glomerular filtration rate. Other studies, such as Riace and Mind It, confirm this. In the world, women with diabetes are systematically under-treated with drugs for CV risk factors, such as ASA, ACE-I, β-blockers, statins, and hypoglycemic agents, and this may explain the failure to achieve the targets. On the contrary, the Italian data are bucking the trend by showing that there are gender differences in the use of these medications. Further studies are needed to investigate biological and non-biological factors, underlying these differences.
Key words: gender, type 2 diabetes, cardiovascular risk.

Differenze di genere nel diabete di tipo 2 (in Italia)

Riassunto. L'impatto del diabete sul rischio cardiovascolare è particolarmente evidente nelle donne, che sono più colpite da eventi cardiovascolari maggiori, soprattutto da infarto, e hanno una mortalità maggiore, confermando la perdita della protezione degli estrogeni anche in età fertile. I dati italiani degli *Annali AMD* hanno documentato che il raggiungimento dei target per i principali fattori di rischio CV è sistematicamente sfavorevole alle donne con diabete T2: in particolare le donne sono più obese, hanno un peggiore compenso del diabete, soprattutto un peggiore profilo lipidico, e una maggior frequenza di riduzione del filtrato glomerulare. Anche i dati dello Studio RIACE e Mind.It sono in accordo. Numerosi studi hanno messo in evidenza che le donne con diabete sono sistematicamente sotto-trattate con i farmaci per il controllo dei fattori di rischio CV, quali ASA, ACE-I, beta-bloccanti, statine, ipoglicemizzanti, e questo può spiegare il mancato raggiungimento dei target. Ma i dati italiani sono in controtendenza dimostrando che non ci sono differenze di genere nell'utilizzo di questi farmaci. Molti fattori biologici, e non solo, non ancora del tutto conosciuti, sottendono queste differenze e vanno esplorati.
Parole chiave: genere, diabete di tipo 2, rischio cardiovascolare.

Gender differences in cardiovascular disease morbidity and mortality in type 2 diabetic subjects

The widely recognized association between type 2 diabetes and cardiovascular disease (CVD) has a different significance according to sex, being stronger in diabetic women compared with men. Diabetic women seem to lose their female advantage toward CVD, being more exposed to this complication irrespective of menopausal status[1,2].

Accordingly, in newly diagnosed diabetic subjects without clinical CVD, carotid atherosclerosis was more prevalent in newly diagnosed diabetic women than in nondiabetic female controls[3], thus confirming the loss of the protective effects of estrogens on the vascular bed also at early stages of the disease.

A meta-analysis of 37 prospective cohort studies investigated the risk of fatal coronary heart disease (CHD) in type 2 diabetes in a total of 447,064 patients[4]. The results of this analysis indicated a higher rate of fatal CHD events in diabetic compared with non-diabetic subjects (5.4 vs 1.6%), but more interestingly a 50% higher relative risk for fatal events in diabetic women than in diabetic men (RR 3.50, 95% CI 2.70-4.53 vs 2.06, 1.81-2.34; P <0.0001).

The higher mortality for CHD in diabetic women was found also in a recent population study[5]: an excess of cardiovascular mortality risk was observed in diabetic patients of both genders; however, this risk was greater in females than males (males: IRR 1.56; 95% CI 1.38-1.76; females: IRR 1.69; 95% CI 1.47-1.93; Wald test for interaction, p = 0.1266).

Also data on stroke emphasizes the greater risk in di-

- Copyright - Il Pensiero Scientifico Editore downloaded by IP 18.97.14.82 Sat, 05 Sep 2026, 20:04:32

abetic women. Data from a registry study in Italy found that in more advanced ages diabetic women were more exposed than men, due to the slower age-related risk reduction in the female sex[6].

Despite this increasing amount of data indicating the higher diabetes-related CVD risk in women, reasons underlying this excess of risk are largely undetermined, potentially including a higher prevalence of common risk factors, difference in hormonal effects and several non-biological factors[7-9].

In this respect, the incidence and predictors of CHD events in type 2 diabetes were investigated in 11,644 CHD-free diabetic patients (6,032 women and 5,612 men) during 4 years of follow-up in the DAI (Diabetes and Informatics Study Group) study[10].

In this survey, the rate of major CHD events was more frequent in diabetic men compared with women (28.8% vs 23.3%), but the women-to-men gradient was 50% higher than the general population and in line with the trend of previous studies indicating a stronger impact of diabetes on CHD in women than men. Also, a recent observational study[11] investigated sex differences in the association between type 2 diabetes and incidence of major cardiovascular diseases, i.e., myocardial infarction, stroke, and heart failure, using the diabetes registry information: in this study, women with T2 diabetes had 1.8 times the probability of a stroke compared with women without diabetes (95%CI 1.60-2.04), 2.6 times of having a myocardial infarction and heart failure (95% CI 2.22-2.99 and 2.27-2.97, respectively). The excess risk for myocardial infarction was significantly higher in T2 diabetic women than in men (IRR 1.78; 95% CI 1.60-1.98; p of interaction < 0.0001), while there is no evidence of sex difference for stroke and heart failure (p = 0.9197 and p = 0.9245, respectively).

The stronger impact of diabetes as a major risk factor for CVD events in women than in men (OR 4.3, 95% CI 3.5-5.2 vs 2.7, 2.7-3.0) was also described by INTERHEART, an international case-control study, including 15,152 cases and 14,820 controls from 52 countries[12].

The evidence that risk factors for CHD may be different in diabetic women comes also from another small study that assessed common and emerging risk factors in a selected group of postmenopausal type 2 diabetic women with (n = 36) and without CHD (n = 59), not taking lipid-lowering medications. This study showed that, besides LDL-C, lower creatinine clearance and small dense LDL particles were the strongest independent risk factors for CHD[13].

In spite of all these epidemiological studies, factors underlying excessive CVD risk in type 2 diabetic women have not been fully elucidated yet[9], although there are definitely numerous biological and non-biological factors that may contribute.

Gender differences in type 2 diabetes: the AMD Annals Initiative

In Italy, a continuous improvement effort by a network of diabetes clinics has been implemented since 2006 under the aegis of the AMD (Associazione Medici Diabetologi)[14-16]. The initiative, which includes approximately one-third of all diabetes outpatient clinics operating within the Italian national healthcare system, allows the monitoring of a large set of process and outcome indicators and the use of specific classes of drugs, with the aim of examining strengths and limitations of current diabetes care in Italy. We used the AMD Annals data to evaluate whether gender differences exist in quality of care in Italy, and specifically in the achievement of cardiovascular risk factor targets or in pharmacological treatments[17]. Overall, 415,294 patients from 236 diabetes outpatient centers were evaluated, of whom 188,125 (45.3%) were women and 227,169 (54.7%) were men. We found that gender disparities are less pronounced in Italy than in other countries[18,19], but they still exist, despite equal access to specialist care and universal coverage of healthcare costs: the Italian Care Model for diabetics could play a role in this. The model mainly consists of a public network of about 600 diabetes clinics, delivering diagnostic confirmation, therapy, prevention, early diagnosis, and medical management of complications through regular patient follow-up by a dedicated team of specialists. Most patients are referred to these care units by their GP, and care is free of charge.

The likelihood of achieving specific clinical outcomes is systematically unfavorable for women as compared with men (Figure 1); specifically, women were 14% more likely than men to have HbA1c >9.0% in spite of insulin treatment (OR = 1.14; 95% CI 1.10-1.17), 42% more likely to have LDL-cholesterol ≥130 mg/dl (OR = 1.42; 95% CI 1.38-1.46) in spite of lipid-lowering treatment, and 50% more likely to have BMI ≥30 kg/m^2 (OR = 1.50; 95% CI 1.50-1.54).

Gender differences in glycemic control

Female outpatients participating in the AMD Annals Initiative were older (30.5% of women vs 20.8% of men were over 75 years of age), had a slightly higher diabetes duration (11.1 ± 9.8 vs 10.0 ± 9.1 years), and were more obese (average BMI 29.2 ± 4.6 kg/m^2 in men vs 30.2 ± 5.9 kg/m^2 in women) then male counterparts. After adjustment for these factors, women were 11% more likely than men to have HbA1c levels >8.0% (64 mmol/mol), 41% more likely to have LDL-C levels ≥130 mg/dl, 50% more likely to have a BMI ≥30 kg/m^2, and 32% more likely to have a glomerular filtration rate (GFR) ≤60 mL/min, whereas women were 48% less likely than

- Copyright - Il Pensiero Scientifico Editore downloaded by IP 18.97.14.82 Sat, 05 Sep 2026, 20:04:32

men to have micro/macroalbuminuria. No differences were found in blood pressure targets. The proportion of patients reaching the HbA1c target was in favor of men in the Italian study[17], in line with other studies in Italy and Europe[19,20].

Table 1 shows that sex disparities are more evident in older people (>75 years), particularly with reference to reaching HbA1c targets. In fact, when the analyses were performed separately in individuals below and over 75 years of age, gender disparities were still documented in younger people, but they were more marked in elderly patients[17], in spite of diabetic treatment.

Gender differences in lipid profile

The lipid profile is worse in women: total cholesterol levels are higher, and more women (+7.2%) do not reach the LDL-C target (<100 mg/dl) as compared with men, particularly in the subgroup treated with lipid-lowering medications[21]; in order to better explore age- and gender-related differences in LDL-C management, these data showed that more women did not reach the LDL-C target when compared with men, and this between-gender gap in reaching LDL-C targets increased with age and diabetes duration, favoring men in all groups (Figure 2). However, the most striking finding of this study was that, unlike men, T2DM women were not able to reach the recommended LDL-C targets, in spite of a similar rate in the use of medications and the same use of statins (41.2% of women and of men). Furthermore, it was demonstrated that women with type 2 diabetes have an HDL-C subpopulations profile shifted toward small dense – and hence less atheroprotective – particles, similar to the finding in diabetic men who have suffered myocardial infarction[22].

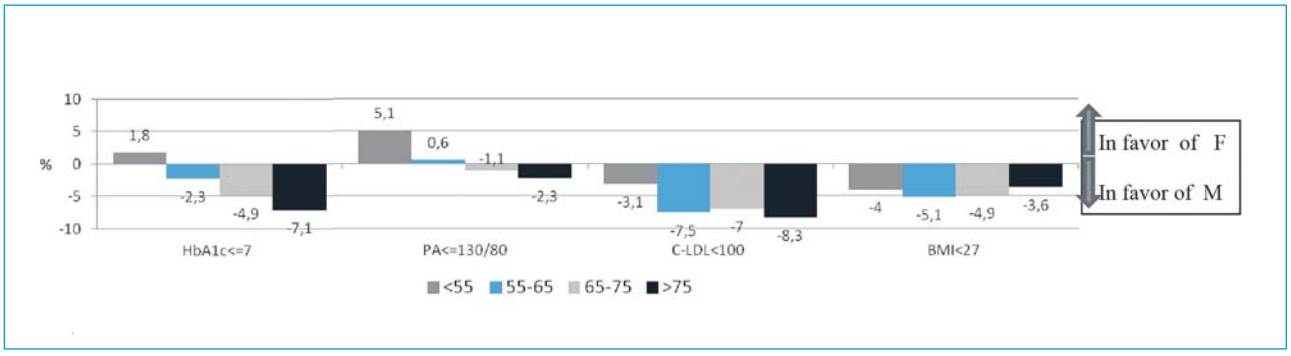

Figure 1. Favorable outcomes in diabetic men and women and age (*AMD Annals*). The intermediate outcomes (target of HbA1c, PA, C-LDL, BMI) are systematically in favor of men, independently of age.

Table 1. Clinical characteristics and treatment, by sex and age. Modified from Rossi MC et al, 2013[17].

	Overall		Age <75 yrs		Age ≥75 yrs	
Diabetic characteristics	**M**	**F**	**M**	**F**	**M**	**F**
N°	227,169	188,125	179,807	130,518	47,210	57,230
Age (years) (X ± SD)	65.7 ± 11.1	68.4 ± 11.4	61.9 ± 9.2	63.1 ± 9.2	79.8 ± 3.7	80.6 ± 4.1
Diabetes treatment (%)						
Diet	7.8	6.4	8.0	6.8	7.2	5.5
Oral agents	63.4	60.4	65.0	63.0	57.4	54.6
Oral agents + Insulin	13.3	16.7	13.5	17.0	12.6	16.1
Insulin	15.5	16.4	13.6	13.1	22.8	23.8
Lipid lowering agents	41.2	41.2	42.2	43.0	37.3	37.5
Antihypertensive treatment	56.6	61.0	54.6	58.3	64.3	67.3
≥2 antihypertensive agents	33.0	36.1	36.4	41.1	46.7	53.1

- Copyright - Il Pensiero Scientifico Editore downloaded by IP 18.97.14.82 Sat, 05 Sep 2026, 20:04:32

Gender differences in pharmacologic treatment

A number of international studies documented systematic under-treatment of cardiovascular risk factors in diabetic women: men with diabetes were significantly more likely to receive treatment for major CVD risk factors, including oral hypoglycemic agents, ACE inhibitors and calcium channel blockers for CHD, than women. Therefore, worse glycated hemoglobin control, lower frequency of lipid-lowering therapy, lower aspirin use, and lower blood pressure control were noted in women[23]. The Canadian Acute Coronary Syndrome Registry I and II demonstrated gender disparity in the intensity of cardiovascular risk reduction, and an underutilization of therapy for acute coronary syndrome treatment[24]. In contrast with these international data, women with diabetes in Italy are not undertreated with medications for cardiovascular risk factors: in the study by Rossi et al.[17], gender differences in CV risk factor targets do not seem to be explained by a lower propensity of physicians to treat women. In fact, women were more likely than men to be treated with insulin and antihypertensive agents and equally likely to be treated with lipid-lowering drugs in the presence of elevated values. Previous research demonstrated the existence of gender differences in drug responses, due to differences in pharmacodynamics and pharmacokinetics[25]. On this issue, a study documented that statin therapy after acute myocardial infarction is associated with reduced rates of all-cause and cardiac mortality, but the degree of risk reduction is lower for women than for men[26].

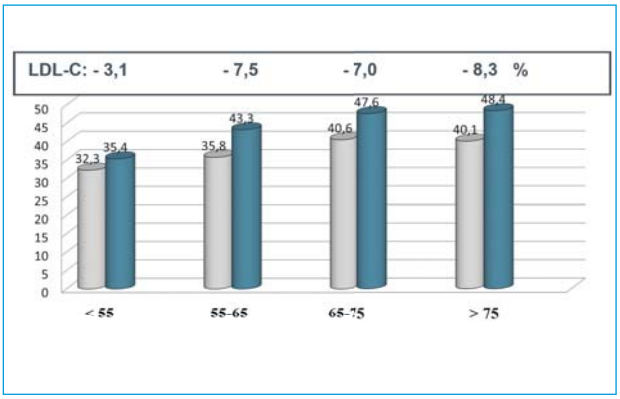

Figure 2. Target of LDL-C in men (blue) and women (grey) and age. The intermediate outcomes (target of HbA1c, PA, C-LDL, BMI) are systematically in favor of men, independently of age. The proportion of men and women with LDL-C target value is unfavorable to women, and the gap increases with age.

Furthermore, women experience a higher incidence of adverse drug reactions than men. Gender-specific differences in the pharmacokinetics and pharmacodynamics of drugs are still unclear[27].

Gender differences in quality of care

In the Italian study, overall cardiovascular risk is higher in diabetic women who are older and more obese and have a slightly longer diabetes duration and, overall, show a worse glycemic control and lipid profile as compared with men, in spite of similar or more intensive pharmacological treatment.

The Q score, based on a combination of process and outcome indicators (Table 2) relative to HbA1c, blood

Table 2. Q score: overall quality of care in T2 diabetes. MA, microalbuminuria.

Quality of care indicator	Scoring
HbA_{1c} measurement <1/year	5
HbA_{1c} ≥8.0%	0
HbA_{1c} <8.0%	10
Blood pressure measurement <1/year	5
Blood pressure values ≥140/90 mmHg, irrespective of treatment	0
Blood pressure values <140/90 mmHg	10
Lipid profile measurement <1/year	5
LDL cholesterol ≥3.37 mmol/L (130 mg/dL) irrespective of treatment	0
LDL cholesterol <3.37 mmol/L (130 mg/dL)	10
MA measurement <1/year	5
Not treated with ACE-inhibitors despite the presence of MA	0
Treated with ACE-inhibitors in the presence or absence of MA	10
Score range	**0-40**

- Copyright - Il Pensiero Scientifico Editore downloaded by IP 18.97.14.82 Sat, 05 Sep 2026, 20:04:32

pressure, LDL-cholesterol and microalbuminuria, was developed and validated in two previous studies[28,29] and ranges between 0 and 40 (the higher the score, the better the quality of care). The two validation studies documented that the risk of developing a new cardiovascular event was 80% higher in patients with a score <15 and 20% higher in those with a score between 15 and 25, as compared with those with a score >25. In this population of type 2 diabetes, the analysis of overall quality of care, as summarized by the Q score, shows that women had a 17% greater likelihood of having a score <15 (OR = 1.10; 95% CI 1.14-1.20) and a 11% lower likelihood of having a score >25 (OR = 0.89; 95% CI 0.87-0.90) as compared with men (Figure 3)[17].

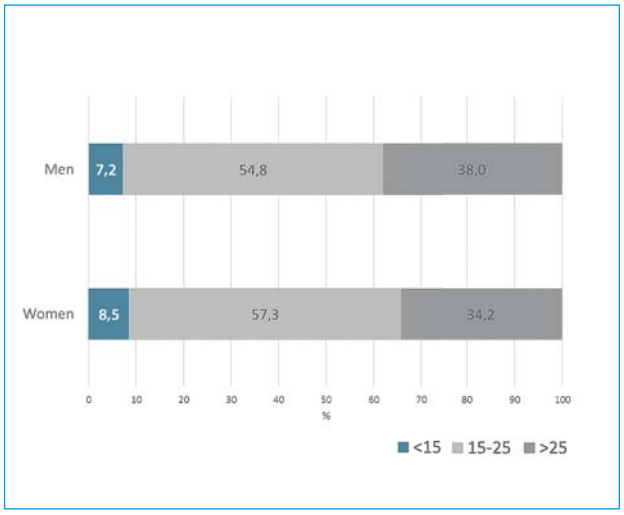

Figure 3. Q score in T2 diabetic patients by gender. Women had a 17% greater likelihood of having a score < 15 - resulting in a higher risk to develop a new CV event - and an 11% lower likelihood of having a score >25, as compared with men.

Gender differences in type 2 diabetes in other cohorts

The relevance of gender difference in CVD risk factors in diabetic subjects was identified in other Italian scenarios as well. The RIACE (Renal Insufficiency And Cardiovascular Events) is a multicenter observational study that enrolled over 15,000 patients attending 19 Italian diabetes clinics to investigate the impact of renal function on CVD morbidity and mortality in type 2 diabetes[30]. Analysis of data from the RIACE cohort showed gender differences in CVD risk factors distribution, with higher levels of HbA1c, BMI and systolic blood pressure, a worse lipid profile and lower levels of GFR in diabetic women compared with men, together with a lower rate in reaching metabolic targets[31]. This worse control of CVD risk factors in women was not related to a different intensity in treatment, being diabetic women more likely to receive pharmacological treatment for hyperglycemia, dyslipidemia and particularly hypertension compared with men.

These findings were in line with other studies in similar Italian cohorts. The MIND-IT (Multifactorial Intervention in type 2 Diabetes in Italy) is a cross-sectional study that enrolled over 2,000 type 2 diabetic patients without previously described CVD events, investigating the degree of control of CVD risk factors[20]. In this cohort too, diabetic women showed a higher prevalence of obesity and abdominal adiposity and a worse CVD risk profile, with a lower percentage of diabetic women reaching the recommended metabolic targets compared with men, especially for blood pressure, LDL and HDL cholesterol, fasting plasma glucose and HbA1c, independently of the use of medications for CVD risk factors control.

Conversely, at variance with reports from Italian cohorts, other European populations showed gender disparities in medication use. In the DIANA study (Type 2 Diabetes Mellitus: New Approaches to Optimize Medical Care in General Practice)[32], a prospective cohort study of 1,146 patients with type 2 diabetes conducted in south-west Germany, the presence of gender disparities in diabetes and CHD medication was evident: the results indicated that men with diabetes were significantly more likely to receive any treatment for major CVD risk factors, including oral hypoglycemic agents, ACE inhibitors and calcium channel blockers for CHD than women. Particularly, men had 53% greater odds to be treated with any antidiabetic drug (95% CI: 1.17 – 1.99), compared with women. The same trend was also seen for aspirin prescription, which showed gender-specific differences, unrelated to the presence of CHD.

Besides, potential under-treatment of CVD risk factors in European women, which may explain the observed stronger impact of CVD risk factors in diabetic women, is not yet completely clear and many factors may play a role. Among these, a different impact of specific risk factors in diabetic women is the main hypothesis to explain the high CVD risk in diabetic women: besides differences in LDL-C levels and management in diabetic men and women, several lines of evidence indicate that modifications in the levels and/or structure of other lipoprotein fractions may play an important role in determining CVD risk, especially in diabetic women[22].

Atherogenic dyslipidemia (i.e., high triglycerides and low HDL-C levels) is usually more frequent in diabetic women than non-diabetic ones, including after adjustment by age and body weight[22,33]. Low levels of HDL-C seem to have a peculiar role on CVD risk in this population. Therefore, findings in the general population indicate that qualitative modifications of HDL particles may influence CVD risk. HDL is a heterogeneous

- Copyright - Il Pensiero Scientifico Editore downloaded by IP 18.97.14.82 Sat, 05 Sep 2026, 20:04:32

class of lipoproteins differing in size, density, charge, and composition and some authors have demonstrated that HDL qualitative properties may strongly modulate CHD risk[34] beyond HDL-C levels. These same modifications toward a less atheroprotective HDL pattern have been recently demonstrated also in a group of type 2 diabetic women who showed, when compared with non-diabetic subjects, lower levels of large α-1, α-2, and pre-α-1 HDL particles, and a higher concentration of small α-3 HDL particles, as determined by two-dimensional gel electrophoresis[22]. Notably, these modifications in HDL subclass profile in diabetic women without CHD were comparable both quantitatively and qualitatively with those found in men with coronary heart disease[35]. Modifications of HDL particles may also influence their functions, including those unrelated to reverse cholesterol transport, such as anti-inflammatory or anti-oxidant properties. This hypothesis was explored in a group of CHD-free women with and without diabetes[36], where the more atheroprotective larger HDL subclasses inversely correlated with circulating levels of the common inflammatory markers hsRCP and IL-6[36,37].

Among 30,000 women and men with T2DM, women with HbA1c levels ≥8.0% had a significantly elevated risk of stroke, whereas men did not[38], but strict blood glucose control has not been shown to decrease the incidence of stroke[39]. One reason could be a potential difference in women and men receiving treatments for hyperglycemia and other CVD risk factors. Even in the previously described studies indicating that women were more treated than men, many other factors play a role: differences in biology, culture, lifestyle, environment and psychosocial factors are simultaneously responsible for sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus[40].

AMD is contributing to the debate on gender-specific diabetes interventions through the regular evaluation of quality of care indicators, which represents the first fundamental step to identify areas in need of improvement. Furthermore, in the context of the DAWN-2[41] initiatives in Italy, AMD is promoting the BENCH-D study[42], aiming to assess psychosocial characteristics and adherence to treatments of type 2 diabetics. In this study, women showed a higher prevalence of poor psychological well-being and likelihood of depression than men; the study also showed that lower levels of psychological well-being were associated with lower levels of satisfaction with treatment, diabetes empowerment and self-care attitudes, and to a worse perception of barriers to medication. The importance of psychosocial factors in addition to biological ones on diabetes outcomes in women has been increasingly recognized, considering that the growing trend in obesity in women is an important marker[40].

Gender differences in mortality

In a recent population study in Italy[5], diabetes determines a 68% excess of mortality rate. Among the causes of CVD, it was observed that excess mortality for AMI was more pronounced in females than males in diabetes (males: IRR 1.48; 95% CI 1.10–1.99; females: 1.81; 95% CI 1.27–2.59; Wald test for interaction, p = 0.1063). In the kidney dysfunctions group – e.g., glomerular diseases, acute kidney failure, chronic kidney disease – the excess of mortality from renal causes in the diabetic population was once again more evident in females than males (males: IRR 1.37; 95% CI 0.88–2.14; females: 2.37; 95% CI 1.43–3.91; Wald test for interaction, p = 0.1466). Myocardial infarction occurs earlier in women with diabetes compared with men[43,44], with higher mortality[5]. According to our data, in a Finnish cohort study[43], the presence of diabetes reduced the so-called female advantage for CVD risk; indeed, mortality from CHD was three times higher in women compared with men with diabetes[5,45].

Conclusions

In women with type 2 diabetes, the risk of major cardiovascular events is anticipated by 20-30 years compared with the population without diabetes, while in men the incidence is anticipated by 15-20 years[11].

In the vast majority of studies, diabetic women were less likely to reach the recommended targets for CV risk factors, as well as to receive treatment and monitoring. Constantly, the wider gap was related to the lipid target; women had higher LDL-C levels than men and were less likely to receive lipid-lowering therapy[46,47].

The AMD Annals data[17] strongly suggests that the greater difficulty in reaching LDL-C targets in diabetic women – despite the same use of lipid-lowering drugs by sex – is mainly related to pathophysiological factors, whereas patient and physician attitudes can play an important role in other process measures and outcomes. Other possible intrinsic pathophysiological gender differences are the impairment of renal function that follows different pathways with a higher prevalence of microalbuminuria in men and more frequently reduced GFR in women[30], as also documented in our study[17], and a higher mortality rate in diabetic women for kidney disease[5].

The results of many studies support the hypothesis that the worse lipid profile is an important cause of a higher risk of CVD in women, and underscore the need for diversifying care by gender. Otherwise, reaching optimal blood pressure, LDL and HbA1c levels simultaneously is rare in diabetic patients, but it is associated with a significantly lower (62%) cardiovascular risk (41%,

- Copyright - Il Pensiero Scientifico Editore downloaded by IP 18.97.14.82 Sat, 05 Sep 2026, 20:04:32

56%, 60% for CHD, respectively)[48]. The answer to the question of whether sex steroids influence the different risk factor levels and clustering of CVD risk factors in women and men remains uncertain[49].

Much is still unknown about gender differences in the cardiovascular consequences of diabetes. Further research – enrolling a high number of women – is required to improve knowledge about the mechanisms underlying gender differences in diabetic patients and to identify the main areas of intervention. The recent study by Legro[50], in fact, indicates that in clinical trials of type 2 diabetes medications, exclusion criteria affecting women of childbearing potential are often disproportionate to risk to the participant and fetus .

It is therefore necessary to continue the study and monitoring of the desirable increase in equity in the quality of care over time in order to reduce the risk of CVD and death in diabetic women[49].

Key messages

- Gender-differences have been reported in diabetic patients: in Italy they are less pronounced than in other countries, but it exists despite equal access to specialist care.
- The likelihood to reach metabolic targets (HbA1c, LDL-C, BMI, PA) is systematically unfavorable in diabetic women as compared with men.
- Diabetic women have a worse lipid profile than men, and have a 2-fold higher CHD risk compared with men. Myocardial infarction occurs earlier and has higher mortality in women with DM compared with men.
- Diabetic women are systematically undertreated with CV therapy, such as ASA, ACE – I, β-blockers, hypoglycemic agents, but not in Italy.
- Pathophysiological factors are involved in the greater difficulty to reach LDL-C targets in diabetic women, despite the same drug treatment in Italy.

Conflict of interest statement: the Authors declare no potential conflits of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

References

1. Mascarenhas-Melo F, Marado D, Palavra F, et al. Diabetes abrogates sex differences and aggravates cardiometabolic risk in postmenopausal women. Cardiovasc Diabetol 2013; 9:12:61.
2. Steinberg HO, Paradisi G, Cronin J, et al. Type II diabetes abrogates sex differences in endothelial function in premenopausal women. Circulation 2000; 101: 2040-6.
3. Catalan M, Herreras Z, Pinyol M, et al. Prevalence by sex of preclinical carotid atherosclerosis in newly diagnosed type 2 diabetes. Nutr Metab Cardiovasc Dis 2015; 25: 742-8.
4. Huxley R, Barzi F, Woodward. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ 2006; 332: 73-8.
5. Ballotari P, Chiatamone Ranieri S, Luberto F, et al. Sex differences in cardiovascular mortality in diabetics and non-diabetic subjects: a population-based study (Italy). Int J Endocrinol 2015; 2015: 914057.
6. Policardo L, Seghieri G, Francesconi P, et al. Gender difference in diabetes-associated risk of first-ever and recurrent ischemic stroke. J Diabetes Complications 2015; 29: 713-7.
7. Rivellese AA, Riccardi G, Vaccaro O. Cardiovascular risk in women with diabetes. Nutr Metab Cardiovasc Dis 2010; 20(6): 474-80.
8. Russo GT, Baggio G, Rossi MC, Kautzky-Willer A. Type 2 diabetes and cardiovascular risk in women. Int J Endocrinol 2015; 2015:832484. doi: 10.1155/2015/832484. Epub 2015 Mar 26.
9. Kautzky-Willer A, Harreiter J, Pacini G. Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. Endocr Rev 2016; 37(3):278-316.
10. Avogaro A, Giorda C, Maggini M, et al; Diabetes and Informatics Study Group, Association of Clinical Diabetologists, Istituto Superiore di Sanità. Incidence of coronary heart disease in type 2 diabetic men and women: impact of microvascular complications, treatment, and geographic location. Diabetes Care 2007; 30: 1241-7.
11. Ballotari P, Venturelli F, Greci M, Giorgi Rossi P, Manicardi V. Sex differences in the effect of Type 2 Diabetes on Major Cardiovascular Diseases: results from a population-based study in Italy. Int J Endocrinol (in press).
12. Yusuf S, Hawken S, Ounpuu S, et al. INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004; 364(9438): 937-52.
13. Russo GT, Giandalia A, Romeo EL, et al. Lipid and non-lipid cardiovascular risk factors in postmenopausal type 2 diabetic women with and without coronary heart disease. J Endocrinol Invest 2014; 37(3): 261-8.
14. Rossi MC, Nicolucci A, Arcangeli A, et al; Associazione Medici Diabetologi Annals Study Group. Baseline quality-of-care data from a quality-improvement program implemented by a network of diabetes outpatient clinics. Diabetes Care 2008; 31: 2166-8.
15. Nicolucci A, Rossi MC, Arcangeli A, et al; AMD-Annals Study Group. Four-year impact of a continuous quality

- Copyright - Il Pensiero Scientifico Editore downloaded by IP 18.97.14.82 Sat, 05 Sep 2026, 20:04:32

improvement effort implemented by a network of diabetes outpatient clinics: the AMD-Annals initiative. Diabet Med 2010; 27: 1041-8.
16. Giorda CB, Nicolucci A, Pellegrini F, et al. Improving quality of care in people with Type 2 diabetes through the Associazione Medici Diabetologi-annals initiative: a long-term cost-effectiveness analysis. Diabet Med 2014; 31: 615-23.
17. Rossi MC, Cristofaro MR, Gentile S, et al.; AMD Annals Study Group. Sex disparities in the quality of diabetes care: biological and cultural factors may play a different role for different outcomes: a cross-sectional observational study from the AMD Annals initiative. Diabetes Care 2013; 36(10): 162-8.
18. Gouni-Berthold I, Berthold HK, Mantzoros CS, et al. Sex disparities in the treatment and control of cardiovascular risk factors in type 2 diabetes. Diabetes Care 2008; 31: 1389-91.
19. Kautzky-Willer A, Kamyar MR, Gerhat D, et al. Sex-specific differences in metabolic control, cardiovascular risk, and interventions in patients with type 2 diabetes mellitus. Gend Med 2010; 7: 571-83.
20. Franzini L, Ardigò D, Cavalot F, et al. Women show worse control of type 2 diabetes and cardiovascular disease risk factors than men: results from the MIND.IT Study Group of the Italian Society of Diabetology. Nutr Metab Cardiovasc Dis 2013; 23(3): 235-41.
21. Russo GT, Pintaudi B, Giorda C, Lucisano G, Nicolucci A, Cristofaro MR, Suraci C, Mulas MF, Napoli A, Rossi MC, Manicardi V. Age- and Gender-Related Differences in LDL-Cholesterol Management in Outpatients with Type 2 Diabetes Mellitus. Int J Endocrinol 2015; 2015: 957105.
22. Russo GT, Horvath KV, Di Benedetto A, Giandalia A, Cucinotta D, Asztalos B. Influence of menopause and cholesteryl ester transfer protein (CETP) TaqIB polymorphism on lipid profile and HDL subpopulations distribution in women with and without type 2 diabetes. Atherosclerosis 2010; 210: 294-301.
23. Wexler DJ, Grant RW, Meigs JB, et al. Sex disparities in treatment of cardiac risk factors in patients with type 2 diabetes. Diabetes Care 2005; 28 (3): 514-20.
24. Bugiardini R, Yan AT, Yan RT, et al. and Canadian Acute Coronary Syndrome Registry I and II Investigators. Factors influencing underutilization of evidence-based therapies in women. European Heart Journal 2011; 32 (11): 1337-44.
25. Franconi F, Brunelleschi S, Steardo L, Cuomo V. Gender differences in drug responses. Pharmacol Res 2007; 55: 81-95.
26. Karp I, Chen SF, Pilote L. Sex differences in the effectiveness of statins after myocardial infarction. CMAJ 2007; 176: 333- 8.
27. Zopf Y, Rabe C, Neubert A, et al. Women encounter ADRs more often than do men. Eur J Clin Pharmacol 2008; 64: 999-1004 .
28. De Berardis G, Pellegrini F, Franciosi M, et al; QuED (Quality of Care and Outcomes in Type 2 Diabetes) Study Group. Quality of diabetes care predicts the development of cardiovascular events: results of the QuED study. Nutr Metab Cardiovasc Dis 2008; 18: 57-65 .
29. Rossi MC, Lucisano G, Comaschi M, et al; AMD-QUASAR Study Group. Quality of diabetes care predicts the development of cardiovascular events: results of the AMD-QUASAR study. Diabetes Care 2011; 34: 347-52.
30. Solini A, Penno G, Bonora E, et al. Renal Insufficiency And Cardiovascular Events (RIACE) Study Group. Diverging association of reduced glomerular filtration rate and albuminuria with coronary and non-coronary events in patients with type 2 diabetes: the renal insufficiency and cardiovascular events (RIACE) Italian multicenter study. Diabetes Care 2012; 35(1):143-9.
31. Penno G, Solini A, Bonora E, et al. Renal Insufficiency And Cardiovascular Events (RIACE) study, group. Gender differences in cardiovascular disease risk factors, treatments and complications in patients with type 2 diabetes: the RIACE Italian multicentre study. J Intern Med 2013; 274(2): 176-91.
32. Krämer HU, Raum E, Rüter G, et al. Gender disparities in diabetes and coronary heart disease medication among patients with type 2 diabetes: results from the DIANA study. Cardiovasc Diabetol 2012; 27: 11-88.
33. Walden CE, Knopp RH, Wahl P, et al. Sex differences in the effect of diabetes mellitus on lipoprotein triglyceride and cholesterol concentrations. N Engl J Med 1984; 311: 953-9.
34. Cheung MC, Brown BG, Wolf AC, Albers JJ. Altered particle size distribution of apolipoprotein A-I-containing lipoproteins in subjects with coronary artery disease. J Lipid Res 1991; 32: 383-94.
35. Asztalos BF, Cupples LA, Demissie S, et al. High-density lipoprotein subpopulation profile and coronary heart disease prevalence in male participants of the Framingham Offspring Study. Arterioscler Thromb Vasc Biol 2004; 24: 2181-7.
36. Russo GT, Giandalia A, Romeo EL, et al. Markers of Systemic Inflammation and Apo-AI Containing HDL Subpopulations in Women with and without Diabetes. Int J Endocrinol 2014; 2014: 607924.
37. Russo GT, Giandalia A., Romeo EL., Cucinotta D. Gender differences in lipoprotein metabolism. Ital J Gender-Specific Med 2015; 1(2): 58-65 | DOI 10.1723/2188.23640
38. Zhao W, Katzmarzyk PT, Horswell R, et al. Sex differences in the risk of stroke and HbA(1c) among diabetic patients. Diabetologia 2014; 57: 918-26. doi: 10.1007/s00125-014-3190-3.
39. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358: 2545–59.
40. Kautzky-Willer A, Harreiter J, Pacini G. Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. Endocr Rev 2016; 9:er20151137.
41. Nicolucci A, Kovacs Burns K, Holt RI, et al. DAWN2 Study Group. Diabetes Attitudes, Wishes and Needs second study (DAWN2™): cross-national benchmarking of diabetes-related psychosocial outcomes for people with diabetes. Diabet Med 2013; 30(7): 767-77.
42. Nicolucci A, Rossi MC, Gentile S, et al; Bench-D Study Group. Correlates of Psychological Well-being in Individuals with Type 2 Diabetes. 72th Scientific Session,

- Copyright - Il Pensiero Scientifico Editore downloaded by IP 18.97.14.82 Sat, 05 Sep 2026, 20:04:32

American Diabetes Association, June 8-12, Philadelphia, PA 2012:A208, 821-P.
43. Hu G, Jousilahti P, Qiao Q, Katoh S, Tuomilehto J. Sex differences in cardiovascular and total mortality among diabetic and non-diabetic individuals with or without history of myocardial infarction. Diabetologia 2005; 48 (5): 856-61.
44. Juutilainen A, Kortelainen S, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Gender difference in the impact of type 2 diabetes on coronary heart disease risk. Diabetes Care 2004; 27 (12): 2898-904.
45. Preis SR, Hwang SJ, Coady S, et al. Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham Heart Study 1950 to 2005. Circulation 2009; 119 (13): 1728-35.
46. Vimalananda VG, Miller DR, Palnati M, et al. Gender disparities in lipid-lowering therapy among veterans with diabetes. Womens Health Issues 2011;21 (Suppl): S176-S181
47. Kim C, Kerr EA, Bernstein SJ, Krein SL. Gender disparities in lipid management: the presence of disparities depends on the quality measure. Am J Manag Care 2006; 12: 133-6.
48. Wong ND, Zhao Y, Patel R, et al. Cardiovascular Risk Factor Targets and Cardiovascular Disease Event Risk in Diabetes: A Pooling Project of the Atherosclerosis Risk in Communities Study, Multi-Ethnic Study of Atherosclerosis, and Jackson Heart Study. Diabetes Care 2016; 39(5): 668-76. doi: 10.2337/dc15-2439. Epub 2016 Mar 29.
49. Regensteiner JG, Golden S, Huebschmann AG, et al. AHA Scientific Statement - Sex Differences in the Cardiovascular Consequences of Diabetes Mellitus. A Scientific Statement From the American Heart Association. Circulation 2015; 132: 2424-47.
50. Phelan AL, Kunselman AR, Chuang CH, Raja-Khan NT, Legro RS. Exclusion of Women of Childbearing Potential in Clinical Trials of Type 2 Diabetes Medications: A Review of Protocol- Based Barriers to Enrollment. Diabetes Care 2016; 39(6): 1004-9. doi: 10.2337/dc15-2723.

Correspondence to:
Valeria Manicardi, MD
Departement of Internal Medicine
Hospital of Montecchio,
AUSL of Reggio Emilia
Tel +39 3393949166
email valeria.manicardi@ausl.re.it