Ital J Gender-Specific Med 2020; 6(3): online ahead of print

Gender differences in cardiovascular risk factors

Elisa Lodi, Omar Stefani, Letizia Reggianini, Alberto Carollo, Valentina Martinotti, Maria Grazia Modena

P.A.S.C.I.A., University of Modena and Reggio Emilia, Italy

Summary. Cardiovascular disease (CVD) has been traditionally considered a purely male disease, and for many years it has been under-estimated and under-recognized in women. Nevertheless, CVD represents the leading cause of female mortality and disability in developing countries. The increased interest in this field allowed for the description of the differences in terms of clinical presentation, prevention, treatment, and prognosis. The recognition of the gender differences in CVD plays an essential role in CVD prevention. Just as a child cannot be considered a small adult, similarly a woman should not be considered a small man, although, at this time, CVD therapy has been studied mainly on male models, and only subsequently administered to women. We should not underestimate the biological and hormonal differences between the sexes, which can affect the various clinical pictures and drug responses. Since CVD is mostly preventable, this review aims to provide an overview on the cardiovascular risk factors in women, focusing on traditional risks, affecting both sexes, though with different relative risk and prevalence, and on the novel and unique risks in women, as this knowledge would help optimize prevention, treatment and prognosis.

Key words. Cardiovascular disease, risk factors, gender differences.

Differenze di genere nei fattori di rischio cardiovascolare: una review

Riassunto. La malattia cardiovascolare (MCV) è stata tradizionalmente considerata una malattia maschile e per molti anni è stata sottovalutata nelle donne. In realtà rappresenta la principale causa di mortalità e disabilità femminile nei paesi in via di sviluppo. Inoltre, sempre più ampiamente, sono state descritte differenze tra maschi e femmine per quanto riguarda i sintomi, il trattamento e la prognosi della MCV. Proprio come un bambino non può essere considerato un piccolo adulto, così la donna non deve essere considerata un piccolo uomo, anche se fino ad oggi la maggior parte delle conoscenze riguardanti la MCV sono derivate da studi condotti principalmente su soggetti di sesso maschile. Ignorare le differenze biologiche ed ormonali tra i due sessi significa sottostimare che esistano quadri clinici diversi e diverse risposte alla terapia. La MCV, inoltre, è una patologia ampiamente prevenibile. Questa review mira a fornire una panoramica dei fattori di rischio cardiovascolare nelle donne: da quelli comuni ai due sessi, che differiscono tuttavia in termini di rischio relativo e prevalenza, a quelli specifici e a quelli esclusivi per il sesso femminile, poiché la loro conoscenza ne è presupposto fondamentale per la prevenzione della MCV nelle donne.

Parole chiave. Malattia cardiovascolare, fattori di rischio, differenze di genere.

Introduction

Cardiovascular disease (CVD), traditionally considered a male disease, is the leading cause of death and disability in women in developing countries. Over one-third of the adult female population is affected by heart disease, with at least one death per minute attributed to CVD in 2018.[1] This mortality rate is equivalent to all the deaths for cancer, diabetes, and chronic lung disease combined.

Sex-specific differences in the incidence of CVD were firstly reported over 80 years ago, and the ratio between men and women under the age of 40 with new cardiovascular events was 24:1.[2]

The prevalence of CVD in postmenopausal women equals that in men, becoming even higher after the age of 75. However, in all age groups women with CVD experience relatively worse outcomes compared to men; therefore, young women are less subject to be affected by CVD, but – when affected – they are exposed to a higher rate of death and complications than men. This trend is particularly evident in women over 55, particularly in Afro-Americans, who often have also a worse general prognosis.[3-6]

There are several reasons for this worse outcome; the different symptoms occurring in women[7] may be responsible for a delay in the diagnosis and intervention. Another is the greater number of post-infarction complications, such as congestive heart failure, acute mitral regurgitation, heart rupture and stroke. Finally, women are less likely to undergo urgent revascularization procedures with more related complications. It has also been reported that women receive a suboptimal medical therapy, and suffer from frequent adverse side effects. Many reasons account for all previous observations: women frequently reach an older age than men and,

because of their social and family role, are less likely to undergo a cardiac rehabilitation program.[4]

Despite the evidence, the awareness to be at high risk of CVD and related complications is still low, both among women and the medical community, although awareness has nearly doubled since 1997. A 2012 survey conducted by the American Heart Association (AHA) has shown that only 56% of American women were aware that CVD is the leading cause of death, and only 13% perceived CVD as the major risk. Furthermore, there is a markedly different awareness in terms of race: only 36% of black women and 34% of Hispanic women reported that CVD is the leading cause of death, compared to 56% of white women.[8,9]

CVD is largely preventable, and it has been reported that, in women, lifestyle changes may prevent CVD in about 75% of cases.[10]

This review aims to provide an overview, focusing on novel and unique risk factors (RFs) in the female population, as well as on sex differences in the traditional RFs, since their knowledge would help to optimize the prevention – and therefore also the diagnosis, treatment and prognosis – of CVD in women.

It is impossible to identify a single cause for CVD, which is the result of the number and the weight of each RF. The most important known traditional RFs affect both men and women, but the prevalence and the relative weight of each one is gender-specific.

Non-gender-specific 'traditional' risk factors: the same, but different

Non-modifiable risk factors

Age. CVD develops over the lifespan of an individual; the older people become, the more likely they are to develop CVD. After the age of 40, the risk of developing CVD is 49% for men and 32% for women. More than four out of five – or 81% – of the people dying from CVD are 65 or older. [11]

Family history. Heredity plays a significant role in the development of CVD. People are at a significantly increased risk for CVD when they have family members (especially first-degree – or even second-degree – relatives) who have a history of CVD. The cardiovascular (CV) risk increases with the number of relatives affected, with the age of onset of CVD (specifically, women <60 years of age and men <55 years of age) and with the degree of the relationship.[12]

Sex. The Framingham Heart Study revealed that men experience their first CV event ten years earlier than women (the average age of the first heart attack from CVD is 65.8 for men, and 70.4 for women). Even though this gap tends to narrow with advancing age, as women's risk for CVD increases after menopause, it fails to match the risk level for men.

Race and ethnicity. The prevalence of CVD among African American women (nearly 48%) is much higher than among Caucasian (35%).[11]

Modifiable risk factors

Diabetes mellitus (T2DM). It is estimated to double the risk of CVD. More specifically, a case-control analysis published on *Lancet* found a 2-fold higher hazard ratio for CVD in T2DM subjects.[13] There is a 3-fold excess fatal CVD risk in women with T2DM compared with non-diabetic women;[14] moreover, women with T2DM have a higher adjusted hazard ratio of fatal events compared with T2DM men.[15] In a meta-analysis of over 850,000 subjects, the relative risk for CVD was 44% greater in women with DM than in similarly affected men.[16]

Hypertension. It is the most prevalent and powerful RF for CVD, and while it affects more men than women until 45 years of age, between 45 and 54 the gap between women and men tends to vanish, up to the point that after the age of 55 the rate of hypertensive women is higher than the men's. The relationship between blood pressure and the risk for CVD is 'continuous', and begins at relatively low levels, particularly when associated with other RFs. There is a direct correlation between hypertension and CVD risk: between the age of 40 and 70 years the risk begins to unfold for a blood pressure (BP) of 115/75 mmHg in all age groups,[17] doubling each time the systolic and diastolic BP increase by 20 mmHg and 10 mmHg, respectively.[18]

Dyslipidemia. At 47.1%, it has the highest population-adjusted risk among women, compared with all other known RFs.[19] The reduction of LDL cholesterol with a statin decreases the risk of major CV events and all-cause mortality regardless of age, sex, baseline LDL cholesterol or previous vascular disease (a 1.0 mmol/l reduction in LDL-C lowers CVD mortality and non-fatal miocardial infarction by 20-25%)[20]. Risk reduction occurs also for extremely low LDL-C level.[21] A high concentration of lipoprotein(a) [Lp(a)] is also associated with an increased risk of CVD, although its contribution to prediction remains controversial. In 3 cohorts of women, Women's Health Study, Women Health Initiative and JUPITER, Lp(a) was associated with CVD only among the subjects with high total cholesterol, and the improvement in prediction was minimal.[22]

Smoking. Smoking is a lethal addictive habit. A lifetime smoker has a 50% probability of dying due to smoking, and a 10-year reduction in life expectancy.[23] Among all the causes of death related to smoking, 50% are due to CVD. The 10-year fatal CVD risk is approximately doubled in smokers, and the relative risk for events at 50 years of age is 5-fold higher than in non-smokers.[24] CVD risk increases even with modest and low levels of smoking: there is not a 'safe dose' of smoking.

A recent meta-analysis reported that in all age groups, with the exception of the youngest (30-44), women had a 25% increased risk for CVD due to cigarette smoking compared to men.[25] The combination of smoking with the use of oral contraceptives has a synergistic effect on the CVD risk.[26]

Chronic kidney disease. Its prevalence has increased over past decades, due to population aging worldwide. The patients affected, particularly in case of end-stage renal disease, face an increased risk of mortality, mainly from CVD.[27] The CV risk begins from the early stages, increasing with the progression of the renal dysfunction, up to the point that, in patients with end-stage renal disease, the risk of CVD mortality is 10-100 times greater than in healthy individuals.[28]

Obesity and overweight. In developed countries, more than 2 adults in 3 are considered to be overweight or obese, and the prevalence of obesity is higher in women than men. The simplest way to define overweight and obesity is by determining the body mass index (BMI); a 25 to 29.9 index means overweight, while a BMI above 30 is considered obesity. As reported in the European Society of Cardiology 2016 guidelines, both overweight and obesity are associated with an increased risk of CVD death and all-cause mortality. The impact of obesity on the development of CVD seems to be greater in women than in men. In the Framingham Heart Study, obesity increased the relative risk of CVD in women by 64%, as opposed to 46% in men.[29] Moreover, not only the BMI, but also the fat distribution is important, since intra-abdominal fat carries a higher CVD risk than subcutaneous fat.[30]

Physical activity: it reduces all-cause and CVD mortality by 20-30%, since it has a positive effect on many RFs, including hypertension, LDL/HDL cholesterol, body weight and T2DM in all age subgroups, from childhood to the elderly. High intensity training may be effective for competitive purposes, but is not required for primary prevention, since the additional risk reduction compared with moderate activity is minimal.[31] When compared to women practicing greater levels of physical activity, those performing <4.7 metabolic equivalents of effort in the form of activities of daily living were subject to a 3.7-fold increase in the risk of death or non-fatal CVD.[32] A correct lifestyle based on adequate diet, regular physical activity and weight management is nonetheless both costly and time consuming, and is a tough challenge. Accordingly, women rarely follow such a lifestyle, and this is strongly influenced by their income level, social role, education and culture.[33]

Guidelines cannot provide different ranges for men and women, since this would require new epidemiological studies for all medical societies involved in the European community.

Non-gender-specific 'novel' cardiovascular risk factors

Depression and emotional stress. Women are more depressed than men (prevalence 2:1), and it has been widely demonstrated that chronic emotional stress is a prevalent and increasingly recognized RF, equivalent to smoking and high blood pressure.[34] Furthermore, the presence of depression is a negative prognostic factor in patients with CVD;[35] in fact, it has been shown that people affected by CVD who are depressed have a 4-fold higher risk to die from cardiac causes than those who are not stressed.[36] So, there is actual evidence that depression is a RF and that it leads to a worse outcome in cardiac patients; on the other hand, CVD involves a greater risk of depression and emotional discomfort.[37]

Inflammatory and autoimmune diseases. These are characterized by an improper activation of the immune system. Many studies have demonstrated the association between these diseases and an increase in mortality, mainly as a consequence of CVD. For most systemic autoimmune disorders there is a clear gender difference in prevalence (that is, 2- to 50-fold higher in women, because of the enhancement of the immune system response caused by estrogens), making this a more prevalent RF in women. Growing evidence suggests that inflammatory and autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus, lead to increased CV morbidity and mortality; this is due to a premature and accelerated atherosclerosis, related to the chronic inflammation status with the release of pro-inflammatory cytokines (such as TNFa, IL-1, IL-6), causing pro-atherogenic and pro-thrombotic alterations.[38,39]

Gender-specific risk factors

Most of the burden of CVD can be explained by traditional and 'novel' risk factors affecting men and women alike. In women, there is increasing evidence that several factors related to changes in the hormonal environment may be associated with the risk of CVD later in life;[40] we define these woman-specific risk factors as 'gynecardiological RFs'.

Menarche and menopause. Age at menarche has been reported to be associated with the risk of CVD later in life; according to the results of a large prospective study on UK women, the relation between age at menarche and CVD risk is 'U shaped', with both early and late menarche being associated with an increased risk. Compared with menarche at 13 years of age, menarche at ≤10 and ≥17 years of age was associated with an increased relative risk of 27% and 23%, respectively. [41]

Premenopausal women are relatively protected compared with men of the same age. However, this sex gap narrows down after menopause, and the risk is related to the menopause onset age.

There is recent evidence about an increased nocturnal cortisol excretion, mainly in women after menopause with metabolic syndrome, associated with a low inflammatory state, which still need to be interpreted.[42] Many studies have shown a higher risk of CVD morbidity and mortality in women who experience premature or early-onset menopause.[40,41,44] Women with premature or early-onset menopause may not only be at risk from a younger age, but also live more years of their lives at an increased risk of adverse outcomes.[43]

Polycystic ovary syndrome (PCOS), or Stein-Leventhal syndrome. It is the most common endocrine disorder in women of reproductive age, affecting 6-10% of women in their fertile age,[45] and – according to 2003 Rotterdam criteria – it's a condition defined by two of the three following features: i) oligoovulation or anovulation, ii) clinical and/or biochemical signs of hyperandrogenism, or iii) polycystic ovaries. PCOS has a complex number of systemic effects that leads to a higher risk of metabolic syndrome, and it should therefore be considered as an actual RF.[46]

Pregnancy-related disorders

Spontaneous preterm delivery, defined as birth before 37 weeks of gestation, has been reported to complicate 5 to 12.7% of pregnancies worldwide; it is associated with an increased future maternal CVD risk morbidity and mortality, and the risk is even higher in case of early preterm delivery (<34 weeks).[47,48]

Hypertensive pregnancy disorders, including gestational hypertension (defined as the new onset of hypertension – >140/90 mm Hg – after 20 weeks of gestation in normotensive woman), chronic hypertension (hypertension developed before 20 weeks of gestation), and preeclampsia (defined as the new onset hypertension and proteinuria >0.3 g/24 hours). There is increasing evidence that hypertensive pregnancy disorders – a main cause of maternal morbidity – are also associated with an increased CV risk later in life.[49]

Gestational diabetes is defined as a new diagnosis of glucose intolerance beyond the first trimester of pregnancy.[50] It is associated with a 7-fold increase in the risk of developing T2DM compared to women without dysglycemia during pregnancy, and raises the CVD risk regardless of the subsequent development of T2DM.[51]

Weight gain and loss. Pregnancy is the only normal physiological setting in which body weight increases by ≥20% during a 9-month period. The weight at 1 year postpartum is a stronger predictor of the likelihood of being overweight 15 years later than the weight gained during the pregnancy itself.[48,52] A recent study reported that women not losing – but rather gaining – weight between 3 and 12 months postpartum have an adverse cardiometabolic profile.[53]

Breast arterial calcifications (BACs). Detected during routine mammography, they are considered an incidental finding without clinical importance, since they are not associated with an increased risk of breast cancer, as parenchymal calcification are. Today, there is however an increasing evidence that the presence and extent of BACs are correlated with the extent of coronary artery calcifications on computed tomography scan. Since most women over the age 40 undergo breast cancer screening with mammography, the evaluation of BACs may be a non-invasive approach to risk-stratify women for CVD at no additional cost and/or radiation exposure.[54-56]

Breast cancer. It is the most common cancer among women; CVD and breast cancer are highly connected in terms of risk factors, they share the highest incidence and prevalence in old age and, as such, they can often coexist in the same individual. Advancements in the early detection and breast cancer therapy have resulted in over 90% of women surviving 5 years past their diagnosis of breast cancer. Nonetheless, against an increase in survivorship from breast cancer, in these women there has been an increase in CVD.[57] As a result, CVD represents a clinical challenge in the growing number of cancer survivors, who are disproportionately at risk of cardiac, vascular and metabolic diseases.

Radiotherapy for breast cancer often involves the incidental exposure of the heart to ionizing radiation, which subsequently increases the rate of CVD. The increase is proportional to the mean dose to the heart; a population-based case-control study of major coronary events conducted in Sweden and Denmark showed that the rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per gray of the mean radiation dose delivered, with no apparent threshold. The increase started within the first 5 years after radiotherapy and continued into the third decade after radiotherapy. Moreover, women with pre-existing RF have higher risk from radiotherapy than other women, and women irradiated for cancer of the left breast had higher rates of CVD events than women receiving radiation to the right breast.[58]

Breast cancer patients treated with chemotherapy may be at risk for either or both type I (anthracycline-like agents) and type II (trastuzumab-like agents) cardiotoxicity, for which prevention and monitoring are mandatory.[59-62] A recent clinical trial published by *JACC* on women receiving combination anthracycline-trastuzumab chemotherapy found that the incidence of cardiac dysfunction was decreased by the addition of lisinopril or carvedilol to these patients' therapy. Lisinopril and carvedilol were also associated with longer cardiotoxicity-free survival and fewer interruptions in the trastuzumab therapy.[63]

The endocrine therapy has an important role in the treatment of patients with BC expressing estrogen receptor (ER) or progesterone receptor (PR), and it can be associated with an increased CV risk. In the adjuvant

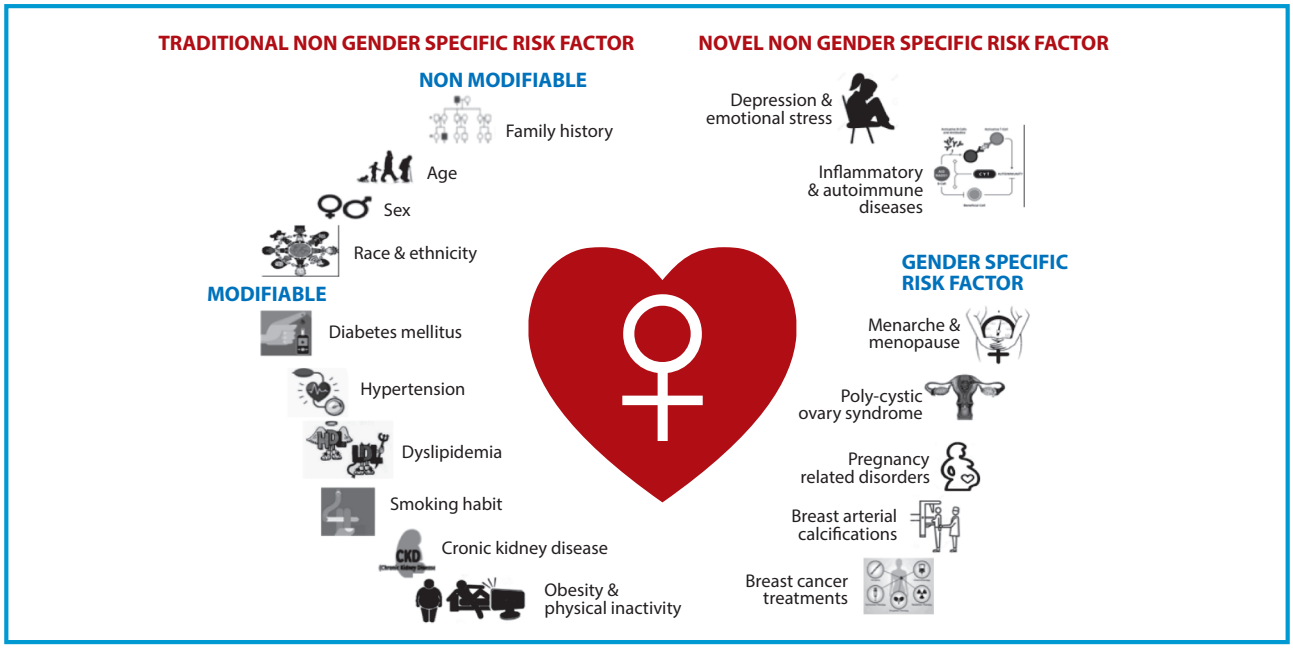

Figure 1. Cardiovascolar risk factors in women.

setting, endocrine therapy is prescribed for an extended period, often ≥5 years. Tamoxifen is the endocrine therapy of choice for premenopausal women, whereas strategies in postmenopausal women can include tamoxifen and/or aromatase inhibitors (AIs). Several studies have shown a trend towards a higher incidence of CV toxicity for AIs compared to tamoxifen which, having a favourable impact on the lipid profile, seems to have a cardio-protective effect.[64]

Thus, it does not mean that women should give up life-saving care; it means that during breast cancer treatment, surveillance, prevention, and the secondary management of cardiotoxicity are crucial, to maximize gains in cancer treatment while minimizing the potential adverse impact on cardiovascular health. In an attempt to provide an optimal therapy and follow-up to women receiving cancer-related treatment, the ESC recently published a position paper which could serve as a useful tool to deal with this complex subject.[65]

Hormone therapy

For oral contraceptives, the CV risk, with the new estroprogestinic combinations, is quite absent, remaining higher only in young smokers.[66] Data on hormone replacement therapy (HRT) are instead still controversial and conflicting.

For many years, in fact, the conventional wisdom, backed by observational and epidemiological studies, has held that the "replacement" of estrogen after menopause would maintain or restore the relative protection from CVD enjoyed by premenopausal women as compared with men of similar age. Controversies about the safety of different postmenopausal hormone therapies started 30 years ago, reaching a peak in 2003, after the publication of the results from the Women's Health Initiative (WHI) trial and the Million Women Study (MWS). These, and later, studies failed to support the benefit of the hormone-replacement therapy either for the secondary (HERS, ERA, WEST) or primary prevention (WHI and MWS) of CVD. Variations in the route of estrogen administration in these trials may be one of the key reasons for the conflicting results. The meta-analysis of 4 available randomized trials (HERS, EVTET, WEST and WHI) indicated that the HRTs tested increased the risk of CV events as early as the first months of use in all postmenopausal women, regardless of age (although the data available on young, healthy, postmenopausal women starting HRT were at that time missing), personal medical history, and ethnic origin. This analysis concluded, moreover, that there was a similar risk in postmenopausal women for all the estrogens administered orally, including the use of estradiol alone, without associated progestin, at the lower dose of 1 mg/d. The first randomised trials on CV prevention resulted therefore in the failure to confirm any CV benefit related to oral estrogen therapy (ET), with a homogeneous trend towards the occurrence of more frequent, more serious and earlier CV accidents in women taking oral formulations compared to those taking a placebo. One possible explanation was the first-pass liver effect of oral administration. After a long period of "scientific silence" on HRT, new studies concluded that symptomatic postmenopausal women willing to start or con-

tinue hormonal treatment, should receive a non-oral route of estradiol as first-line prescription, especially in those at high CV risk.[67] Afterwards, the acronym HRT was changed in MHT (Menopausal Hormonal Therapy), and new data contributed to doubts and hopes on the use of postmenopausal hormones in symptomatic women.

In 2012, a report of the Cache Country Study published in *Neurology* documented that the early use of HRT after menopause, when continued for ten years, reduced the risk of Alzheimer disease of about 30% only in the treated group.[68] In 2015, a meta-analysis of Cochrane on 19 studies observed that HRT started within 10 years after menopause reduces all-cause mortality, myocardial infarction and CV death, concluding that the benefits of HRT were higher than the risk of stroke and venous thromboembolic events.[69] In 2016, the analysis of MHT use in relation to breast cancer incidence in 11 European countries, published in *Maturitas*, reported a drastic decrease in the sales of HRT in all countries, without a reduction in the rate of breast cancer diagnosis.[70] In this regard, a recent study published in *Lancet* showed that breast cancer risk is highly related to the type (every MHT type, except vaginal oestrogens, was associated with excess breast cancer risks which was greater for estrogen-progestogen than estrogen only preparations) and timing (age and duration of assumption) of MHT.[71] In 2018, the results of a large multicenter randomized trial showed that, in the group of women on HRT compared to the group of never users, the risk of colon-rectal cancer was statistically decreased, with a reduction in all-cause mortality.[72]

Our opinion is that MHT should be prescribed early after menopause in symptomatic women, and always in early menopause, if breast cancer risk and family risk are absent.

Key messages

- Cardiovascular disease (CVD) represents the leading cause of premature death and disability in women in developing countries, but the perception of its dangers is still low.
- Specific sexual differences concerning CVD have been described, both in terms of clinical presentation, prevention, treatment and prognosis.
- CVD is largely preventable; identifying the risk factors (RFs) is essential for raising the awareness and preventing CVD.
- Non gender-specific RFs may affect both men and women, but they are different in term of relative risk (hypertension, T2DM, smoking habit, obesity) or prevalence (depression, inflammatory and autoimmune diseases).
- Some RFs are specific to women; we define them 'gynecardiological RFs', since they include reproductive and hormonal factors and others related to the prevention, diagnosis and therapy of breast cancer.

Conclusions

Although CVD remains the most prevalent cause of morbidity and mortality among women, CV risk is often unrecognized, with the consequent absence of an appropriate prevention. As for the CV therapy, also preventive strategies are applied to women, even if derived by trials and the guidelines quite exclusively verified in the male population. There is increasing evidence that the risk factors in women are different, some in terms of prevalence and relative risk, some others because specific of women. Research is on-going in relation to biological and genetic gender-specific differences. In other words, after the era of evidence-based medicine, it is time – especially for women – to develop a personalized medicine to cover the sex gap due to a lack of female enrolment in unrepeatable clinical randomized trials.

References

1. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. Circulation. 2018 20;137(12):e67-e492.
2. Glendy RE, Levine SA, White PD. Coronary disease in youth: comparison of 100 patients under 40 with 300 persons past 80. JAMA. 1937;109(22):1775-81.
3. Bairey Merz CN, Shaw LJ, Reis SE, Bittner V, Kelsey SF, Olson M, et al. Insights from the NHLBI-sponsored women's ischemia syndrome evaluation (WISE) study. Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. J Am Coll Cardiol. 2006;47(3 Suppl):S21-9.
4. Supervía M, Medina-Inojosa JR, Yeung C, Lopez-Jimenez F, Squires RW, Pérez-Terzic CM, et al. Cardiac rehabilitation for women: a systematic review of barriers and solutions. Mayo Clin Proc. 2017;92(4):565-77.
5. Sahni S, Fonarow GC. Gender bias trends in implantable cardioverter-defibrillator therapy. Curr Cardiovasc Risk Rep. 2014;8(3):375.
6. Schoen MW, Tabak RG, Salas J, Scherrer JF, Buckhold FR. Comparison of adherence to guideline-based cholesterol treatment goals in men versus women. Am J Cardiol. 2016;117(1):48-53.
7. Shirato S, Swan BA. Women and cardiovascular disease: an evidentiary review. Medsurg Nurs. 2010;19(5):282-306.
8. Mosca L, Hammond G, Mochari-Greenberger H, Towfighi A, Albert MA. Fifteen-year trends in awareness of heart disease in women. Circulation. 2013;127(11):1254-63.
9. Kling JM, Miller VM, Mankad R, Wilansky S, Wu Q, Zais TG, et al. Go red for women cardiovascular health-screening evaluation: the dichotomy between awareness and perception of cardiovascular risk in the community. J Womens Health. 2013;22(3):210-18.
10. Chomistek AK, Chiuve SE, Eliassen AH, Mukamal KJ, Willett WC, Rimm EB. Healthy lifestyle in the primordial prevention of cardiovascular disease among young women. JACC. 2015;65(1):43-51.

11. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Executive summary: heart disease and stroke statistics 2012 update. Circulation. 2012;125(1):188-97.
12. Barrett-Connor E, Khaw K. Family history of heart attack as an independent predictor of death due to cardiovascular disease. Circulation. 1984;69(6):1065-9.
13. Emerging Risk Factors Collaboration, Sarwar N, Gao P, Seshasai SRK, Gobin R, Kaptoge S, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375(9733):2215-22.
14. Manson JE, Colditz GA, Stampfer MJ, Willett WC, Krolewski AS, et al. A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. Arch Intern Med. 1991;151(6):1141-7.
15. 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.
16. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ. 2006;332(7533):73-8.
17. Lewington S, Clarke R, Qizibash N, Peto R, Collins R. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360(9349):1903-13.
18. Izumi Y, Matsumoto K, Ozawa Y, Kasamaki Y, Shinndo A, Ohta M, et al. Effect of age at menopause on blood pressure in postmenopausal women. Am J Hypertens. 2007;20(10):1045-50.
19. Yusuf S, Hawken S, Ôunpuu S, Dans T, Avezum A, Lanas F, et al. 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.
20. Cholesterol Treatment Trialists' (CTT) Collaborators, Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012;380(9841):581-90.
21. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. New Engl J Med. 2017;376(18):1713-22.
22. Cook NR, Mora S, Ridker PM. Lipoprotein(a) and cardiovascular risk prediction among women. JACC. 2018;72(3):287-96.
23. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ. 2004;328(7455):1519.
24. Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. BMJ. 1998;316(7137):1043-7.
25. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. Lancet. 2011;378(9799):1297-305.
26. Pomp ER, Rosendaal FR, Doggen CJM. Smoking increases the risk of venous thrombosis and acts synergistically with oral contraceptive use. Am J Hematol. 2008;83(2):97-102.
27. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296-305.
28. Herzog CA, Ma JZ, Collins AJ. Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. New Engl J Med. 1998;339(12):799-805.
29. Wilson PWF, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. Arch Intern Med. 2002;162(16):1867-72.
30. Vecchié A, Dallegri F, Carbone F, Bonaventura A, Liberale L, Portincasa P, et al. Obesity phenotypes and their paradoxical association with cardiovascular diseases. Eur J Intern Med. 2018;48:6-17.
31. Löllgen H, Böckenhoff A, Knapp G. Physical activity and all-cause mortality: an updated meta-analysis with different intensity categories. Int J Sports Med. 2009;30(3):213-24.
32. Shaw LJ, Olson MB, Kip K, Kelsey SF, Johnson BD, Mark DB, et al. The value of estimated functional capacity in estimating outcome: results from the NHBLI-sponsored women's ischemia syndrome evaluation (WISE) study. J Am Coll Cardiol. 47(3 Suppl):S36-43.
33. 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. 2019;26(6):609-10.
34. Millett ERC, Peters SAE, Woodward M. Sex differences in risk factors for myocardial infarction: cohort study of UK Biobank participants. BMJ. 2018;363:k4247.
35. Ndrepepa G. Psychological distress and mortality in stable coronary heart disease: persistence of high distress means increased risk. Heart. 2017;103(23):1840-1.
36. Stewart RAH, North FM, West TM, Sharples KJ, Simes RJ, Colquhoun DM, et al. Depression and cardiovascular morbidity and mortality: cause or consequence? Eur Heart J. 2003;24(22):2027-37.
37. Kemp DE, Malhotra S, Franco KN, Tesar G, Bronson DL. Heart disease and depression: don't ignore the relationship. Cleve Clin J Med. 2003;70(9):745-6, 749-50, 752-4 passim.
38. Durante A, Bronzato S. The increased cardiovascular risk in patients affected by autoimmune diseases: review of the various manifestations. J Clin Med Res. 2015;7(6):379-84.
39. Abou-Raya S, Abou-Raya A, Naim A, Abuelkheir H. Chronic inflammatory autoimmune disorders and atherosclerosis. Ann N Y Acad Sci. 2007;1107:56-67.
40. Peters SA, Woodward M. Women's reproductive factors and incident cardiovascular disease in the UK Biobank. Heart. 2018;104(13):1069-75.
41. Canoy D, Beral V, Balkwill A, Wright FL, Kroll ME, Reeves GK, et al. Age at menarche and risks of coronary heart and other vascular diseases in a large UK cohort. Circulation. 2015;131(3):237-44.
42. Martocchia A, Gallucci M, Noales M, Maggi S, Cassol M, Stefanelli M, et al. The cortisol burden in elderly subjects with metabolic syndrome and its association with lowgrade inflammation. Aging Clin Exp Res. 2019. doi: 10.1007/s40520-019-01322-3.
43. Muka T, Oliver-Williams C, Kunutsor S, Laven JS, Fauser BC, Chowdhury R, et al. Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-

cause mortality: a systematic review and meta-analysis. JAMA Cardiol. 2016;1(7):767-76.
44. Sciomer S, De Carlo C, Moscucci F, Maffei S. Age at menopause: a fundamental data of interest to acquire in female patients' anamnesis. Int J Cardiol. 2016;215:358-9.
45. Cho LW, Randeva HS, Atkin SL. Cardiometabolic aspects of polycystic ovarian syndrome. Vasc Health Risk Manag. 2007;3(1):55-63.
46. Scicchitano P, Dentamaro I, Carbonara R, Bulzis G, Dachille A, Caputo P, et al. Cardiovascular risk in women with PCOS. Int J Endocrinol Metab. 2012;10(4):611-8.
47. Kessous R, Shoham-Vardi I, Pariente G, Holcberg G, Sheiner E. An association between preterm delivery and long-term maternal cardiovascular morbidity. Am J Obstet Gynecol. 2013;209(4):368.e1-368.e8.
48. Silverberg O, Park AL, Cohen E, Fell DB, Ray JG. Premature cardiac disease and death in women whose infant was preterm and small for gestational age. A retrospective cohort study. JAMA Cardiol. 2018;3(3):266.
49. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ. 2007;335(7627):974.
50. Association AD. 2. Classification and diagnosis of diabetes. Diabetes Care. 2015;38(Supplement 1): S8-S16.
51. Vrachnis N, Augoulea A, Iliodromiti Z, Lambrinoudaki I, Sifakis S, Creatsas G. Previous gestational diabetes mellitus and markers of cardiovascular risk. Int J Endocrinol. 2012; 2012:458610.
52. Linné Y, Dye L, Barkeling B, Rössner S. Long-term weight development in women: a 15-year follow-up of the effects of pregnancy. Obes Res. 2004;12(7):1166-78.
53. Kew S, Ye C, Hanley AJ, Connelly PW, Sermer M, Zinman B, et al. Cardiometabolic implications of postpartum weight changes in the first year after delivery. Diabetes Care 2014;37(7):1998-2006.
54. Quan Bui, Lori Daniels. A Review of the role of breast arterial calcification for cardiovascular risk stratification in women. Circulation. 2019;139(8):1094-101.
55. Ratti C, Romagnoli R, MG Modena et al. Calcificazioni arteriose mammarie e calcificazioni coronariche: un "link" comune con la malattia aterosclerotica subclinica. Ital Heart J Suppl. 2005;6 (9):569-74.
56. Margolies L, Salvatore M, Hecht HS, Kotkin S, Yip R, Baber U, et al. Digital mammography and screening for coronary artery disease. JACC Cardiovasc imaging. 2016;9(4):350-360.
57. Park NJ, Chang Y, Bender C, Conley Y, Chlebowski RT, Van Londen GJ, et al. Cardiovascular disease and mortality after breast cancer in postmenopausal women: results from the Women's Health Initiative. PLoS ONE. 2017;12(9):e0184174.
58. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013;368(11):987-98.
59. Herrmann J, Lerman A, Sandhu NP, Villarraga HR, Mulvagh SL, Kohli M. Evaluation and management of patients with heart disease and cancer: cardio-oncology. Mayo Clin Proc. 2014;89(9):1287-306.
60. Yeh ETH, Chang HM. Oncocardiology-past, present, and future: a review. JAMA Cardiol. 2016;1(9):1066-72.
61. Eschenhagen T, Force T, Ewer MS, de Keulenaer GW, Suter TM, Anker SD, et al. Cardiovascular side effects of cancer therapies: a position statement from the heart failure association of the european society of cardiology. Eur J Heart Fail. 2011;13(1):1-10.
62. Moslehi JJ. Cardiovascular toxic effects of targeted cancer therapies. N Engl J Med. 2016;375(15):1457-67.
63. Guglin M, Krischer J, Tamura R, Fink A, Bello-Matricaria L, McCaskill-Stevens W, et al. Randomized trial of lisinopril versus carvedilol to prevent trastuzumab cardiotoxicity in patients with breast cancer. JACC. 2019;73(22):2859-68.
64. Mehta LS, Watson KE, Barac A, Beckie TM, Bittner V, Cruz-Flores S, et al. Cardiovascular disease and breast cancer: where these entities intersect: a scientific statement from the american heart association. Circulation. 2018;137(8):e30-66.
65. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, et al. The task force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur J Heart Fail. 2017;19(1):9-42.
66. Weill A, Delichampt M, Raguideau F, Ricorderau P, Blotière PO, Rudant J, et al. Low dose oestrogen combined oral contraception and risk of pulmonary embolism, stroke, and myocardial infarction in five million French women: cohort study. BMJ. 2016;353:i2002.
67. Modena MG. Estrogens and the heart: do they help or hurt? How estrogen impacts the cardiovascular system. SOJ Ginecol Obstet Womens Health. 2016;2(1):2-8.
68. Shao H, Breitner JC, Whitmer RA, Wang J, Hayden K, Wengreen H, et al. Cache Country Investigators. Hormone therapy and Alzheimer disease dementia. Neurology. 2012; 79(18):1846-52.
69. Boardman HM, Hartley L, Eisinga A, Main C, Roqué i Figuls M, Bonfill Cosp X, et al. Hormone therapy for preventing cardiovascular disease in post-menopausal women. Cochrane Database Syst Rev. 2015;(3):CD002229.
70. Antoine C, Ameye L, Paesmans M, de Azambuja E, Rozenberg S. Menopausal hormone therapy use in relation to breast cancer incidence in 11 European countries. Maturitas. 2016;84:81-8.
71. Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet. 2019; 394(10204):1159-68.
72. Symer M, Wong NZ, Abelson JS, Milsom J, Yeao H. Hormone replacement therapy and colorectal cancer incidence and mortality in the prostate, lung, colorectal, and ovarian cancer screening trial. Clin Colorectal Cancer. 2018;17(2): e281-e288.

Author contribution statement: all Authors contributed in conceiving the content and in the final review of the article.

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

Correspondence to:
Maria Grazia Modena
Università degli Studi di Modena e Reggio Emilia
Via del Pozzo 71
41124 Modena, Italy
email: mariagrazia.modena@unimore.it