International Journal of Nutrology
(Official Journal of the ABRAN - Brazilian Association of Nutrology)

REVIEW ARTICLE

DOI: 10.54448/ijn25S404

Major clinical findings hormone replacement therapy and prevention of cardiovascular events: a systematic review

Ana Angélica Nogueira Lima[1*], Carmen Melo do Vale[1], Marcelo Rodrigues Zacarkim[2], Firmino Lucas Barreto de Matos Nobre[3], Lara Maria Vilaça de Figueiredo[3], José de Sousa Xavier[4], Alfredo Máximo Grilo Jardim[5], Ana Gabriella de Almeida Araújo[6], Iago Aum Malaspina[7], Vittor Candido Soares[8]

[1] Potiguar University - Medical School. Natal, Rio Grande do Norte, Brazil.
[2] Lubentium Institute. Pres. Juscelino Kubitschek avenue, 1545 São Paulo, Brazil.
[3] Medfacil. Campos Sales avenue, 901 - Manhattan Business - rooms 1201 e 1202 - Tirol, Natal, Rio Grande do Norte, Brazil.
[4] Mauricio Lacerda Clinic. Ângelo Varela street, 1135, Tirol, Natal, Rio Grande do Norte, Brazil.
[5] SESAP - Monsenhor Walfredo Gurgel Hospital, Senador Salgado Filho avenue, Tirol, Natal, Rio Grande do Norte, Brazil.
[6] Multimed Clinic. Street 3, 1035, setor Oeste, Goiânia, Goiás, Brazil.
[7] Carlos Fernando Malzoni Hospital. Sete de Setembro avenue, 750, Centro, Matão, São Paulo, Brazil.
[8] Mulher Mãe Luzia Hospital. Fab avenue, 81, Central, Macapá, Amapá, Brazil.

*Corresponding authors: Dr. Ana Angélica Nogueira Lima. Potiguar University- Medical School. Natal, Rio Grande do Norte, Brazil.
E-mail: milana7@hotmail.com
DOI: https://doi.org/10.54448/ijn25S404
Received: 07-26-2025; Revised: 09-28-2025; Accepted: 09-28-2025; Published: 10-02-2025; IJN-id: e25S404

Editor: Dr Hind Mamoun Beheiry, MD, MPH.

Abstract

Introduction: Cardiovascular disease (CVD) is the leading cause of death in women. Low estrogen levels during menopause are associated with an increased risk of CVD. Therefore, hormone replacement therapy (HRT) can mitigate menopause-related diseases. Vasomotor symptoms affect about 60.0 to 80.0% of postmenopausal women and may have an incidence of 90.0% in perimenopausal women. The main studies in the last 20 years have investigated the effects of estrogen therapy on symptoms and women's health during menopause. **Objective:** This was to conduct a systematic review to better understand the main findings and discussions of international consensus on hormonal therapies in women regarding cardiovascular events. **Methods:** The systematic review rules of the PRISMA Platform were followed. The research was carried out from May to June 2025 in Scopus, Embase, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument, and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 130 articles were found. A total of 39 articles were fully evaluated, and 23 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 21 studies at high risk of bias and 25 studies that did not meet the GRADE and AMSTAR-2. It was concluded that hormone replacement therapy is a sex-specific and time-dependent primary cardiovascular disease prevention therapy that concomitantly reduces all-cause mortality as well as other aging-related diseases. Observational studies did not suggest an increased risk of myocardial infarction in postmenopausal women with diabetes prescribed HRT. Lipoprotein, LDL-C, and insulin resistance were lower with hormone therapy, and HDL-C levels were higher with hormone therapy compared to placebo. Thus, hormone therapy in women was shown to be important for improving organic functions and quality of life, as well as showing a bias in reducing cardiovascular events.

Keywords: Cardiovascular risk. Women. Menopausal. Hormonal therapy. Hormone replacement.

Introduction

Cardiovascular disease (CVD) is the leading cause of death in women. Low estrogen levels during menopause are associated with an increased risk of CVD. Therefore, hormone replacement therapy (HRT) can mitigate menopause-related diseases, such as CVD. Furthermore, vasomotor symptoms affect about 60.0 to 80.0% of postmenopausal women and may have an incidence of 90.0% in perimenopausal women (1 to 2 years before menopause) **[1,2]**.

With the increase in hypoestrogenism, hypotrophy of the breasts and urogenital apparatus, skin changes, and accelerated bone loss may occur **[3]**. Furthermore, CVD tends to occur more frequently in postmenopausal women. During the reproductive years, estrogen (E2) interacts with estrogen receptors (ERs) on endothelial cells, vascular smooth muscle, and the extracellular matrix, causing genomic and non-genomic effects, including vasodilation, decreased blood pressure, and cardiovascular protection, demonstrating the beneficial effects of female sex hormones on cardiovascular function. Furthermore, the benefits of E2 supplementation in alleviating vasomotor symptoms during menopause have led to clinical investigations of the effects of menopausal hormone therapy (MHT) on CVD **[4]**.

Hypoestrogenism causes an increase in total cholesterol and triglycerides, LDL lipoproteins, and a decrease in HDL. There is also fat accumulation in the visceral region, decreased secretion and sensitivity of the organism to the action of insulin, and compensatory hyperinsulinemia. There is also increased renal sodium reabsorption, increased sympathetic nerve activity, and changes in the vascular bed, with increased blood pressure **[5-7]**.

The main studies in the last 20 years studies to investigated the effects of estrogen therapy on symptoms and women's health in the climacteric. As a major vasomotor symptom, hot flushes affect about 75.0% of Caucasian women and, for the North American Menopause Society (NAMS), hot flushes are the primary indication for hormonal administration **[7,8]**. One study found a reduction in vasomotor symptoms regardless of the estrogen dose associated with progestogen, but higher doses of estrogen alone were more effective in reducing symptoms. In the cardiovascular system, a study with 121,700 nurses verified the reduction of coronary artery disease and mortality in women after the use of estrogen therapy **[9]**.

The formations were not associated with the occurrence of infarctions and strokes. These studies still have limitations. The number of participants is not sufficient to determine the risks of treatment, whether for major cardiovascular events or prostate cancer. There are many benefits, but we do not know the risks yet. Our next step is a longer and longer test to determine if replacement can increase the incidence of heart attack and prostate tumors, and reduce the risk of fractures **[7,8]**.

Therefore, the present study aimed to make a systematic review to better understand the main findings and discussions of international consensus on hormonal therapies in women regarding cardiovascular events.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: May 11, 2025. The AMSTAR-2 (Assessing the Methodological Quality of Systematic Reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: May 11, 2025.

Search Strategy and Search Sources

The literature search process was conducted from May to June 2025 and was based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, covering scientific articles from various periods to the present day. The following health sciences descriptors (DeCS/MeSH Terms) were used *"Cardiovascular risk. Women. Menopausal. Hormonal therapy. Hormone replacement"* and the Boolean "and" between MeSH terms and "or" between historical findings were used.

Study Quality and Risk of Bias

Quality was classified as high, moderate, low, or very low based on the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most prominent articles were systematic reviews or meta-analyses of randomized controlled trials, followed by randomized clinical trials. Low-quality evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. Risk of bias was analyzed according to the Cochrane instrument by analyzing the funnel plot (sample size versus effect size), using Cohen's d test.

Results and Discussion

Summary of Findings

As a corollary to the literature search system, a total of 130 articles were found and submitted to eligibility analysis. Subsequently, 23 of the 39 final studies were selected to comprise the results of this systematic review. The selected studies were of medium to high quality (Figure 1), considering the level of scientific evidence of studies in meta-analysis, consensus, randomized clinical, prospective, and observational studies. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with X^2=87.7%>50%. Considering the Cochrane risk of bias tool, the overall assessment resulted in 21 studies with a high risk of bias and 25 studies that did not meet the GRADE and AMSTAR-2 criteria.

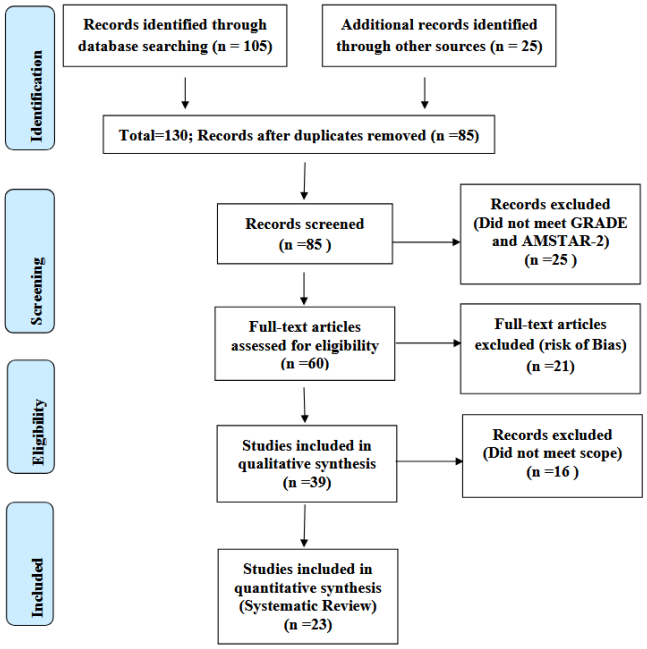

Figure 1. Flowchart showing the article selection process. Source: Own Authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's d Test. The sample size was determined indirectly by the inverse of the standard error (1/Standard Error). This graph showed symmetrical behavior, suggesting no significant risk of bias, either among studies with small sample sizes (lower precision), which are shown at the bottom of the graph, or among studies with large sample sizes, which are shown at the top.

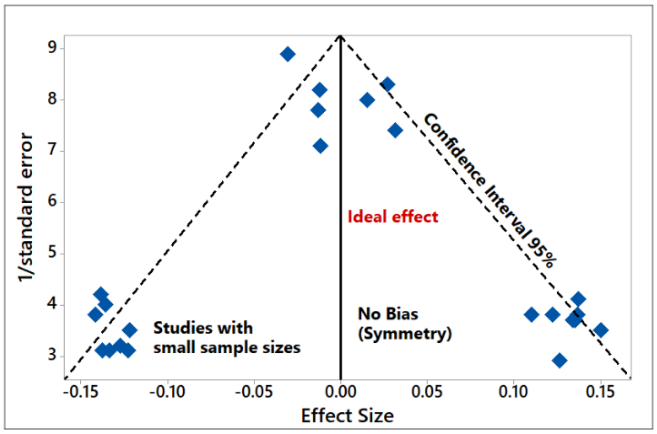

Figure 2. The symmetrical funnel plot suggests no risk of bias among the small sample size studies shown at the bottom of the graph. High-confidence and highly recommended studies are shown above the graph (Ntotal = 23 studies fully evaluated in the systematic review). Source: Own Authorship.

Major Clinical Findings

Hormonal Therapy in Women

Stress, sedentary lifestyle, contraceptive use and irregular diet are some factors that lead to a decrease in testosterone in young women, presenting symptoms such as fatigue, lack of libido, weight gain, difficulty in gaining muscle mass. After menopause testosterone production falls significantly, leading to worsening of these symptoms. Often the woman complains of intense fatigue associated with unexplained discouragement and even depression. Testosterone at optimal levels brings numerous benefits, as shown in Figure 3 **[1-4,7,8]**.

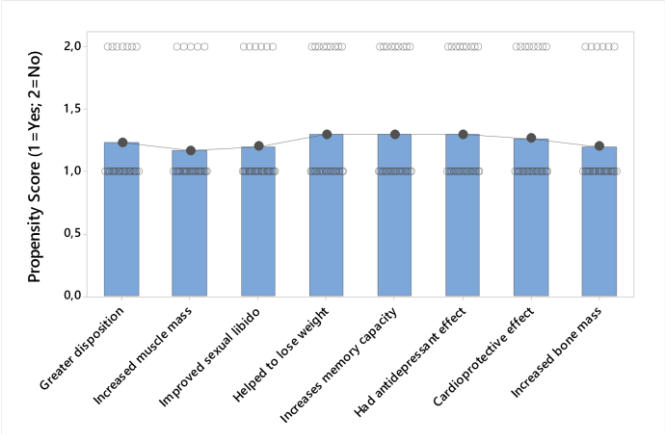

Figure 3. Graph showing the propensity score of the main literary findings of hormonal therapy benefits in women. Source: Own authorship.

Studies show that the effects of hormone replacement therapy (HRT) on menopause are determined by age and/or time since menopause,

underlying target tissue health, and duration of therapy. Once initiated in women under 60 and/or in menopause, HRT can significantly reduce all-cause mortality and CVD compared with lipid-lowering therapy. Risks associated with HRT, including breast cancer, stroke, and venous thromboembolism, are rare (<10 events/10,000 women), are not unique to HRT, and are comparable to other medications. Hormone replacement therapy is a sex-specific and time-dependent primary CVD prevention therapy that concomitantly reduces all-cause mortality as well as other aging-related diseases **[10]**.

The authors Risni et al. (2024) **[11]** analyzed the risk of CVD in postmenopausal women with diabetes using HRT compared with those who did not use it through a meta-analysis. Of the 7,625 articles identified, 19 (6 clinical trials and 13 observational studies) were included. The meta-analysis of the risk of myocardial infarction (MI) from nine observational studies (n = 34,626) showed a pooled RR of 0.83 (95% CI 0.62-1.12). Observational studies did not suggest an increased risk of MI in postmenopausal women with diabetes prescribed HRT.

In addition, the authors Nudy et al. (2025) **[12]** evaluated long-term changes in cardiovascular biomarkers during the WHI (Women's Health Initiative) hormone therapy (HT) clinical trials with conjugated equine estrogens (CEE) alone and CEE plus medroxyprogesterone acetate (MPA). HT trial participants from the CEE alone (n = 1,188, 0.625 mg/d CEE or placebo) and CEE + MDA (n = 1,508, 0.625 mg/d CEE plus 2.5 mg/d MPA or placebo) trials provided blood samples at baseline and after 1, 3, and 6 years. Low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, total cholesterol, lipoprotein(a), glucose, insulin, and the homeostatic model assessment for insulin resistance were measured. During the intervention phase of the CEE-alone trial, randomization to CEE resulted in a 11% reduction in LDL-C over 6 years (geometric mean ratio, 0.89; 95% CI, 0.88-0.91; p < 0.001). The overall reduction in LDL-C was similar for CEE+MPA compared with placebo (geometric mean ratio 0.88, 95% CI 0.86-0.89, p<0.001). Compared to placebo, HDL-C and triglyceride levels were 13.0% and 7.0% higher with CEE and CEE+MPA, respectively. Homeostatic model assessment for insulin resistance decreased by 14.0% and 8.0% for participants in the CEE-alone and CEE+MPA trials, respectively. Compared to placebo, lipoprotein(a) decreased by 15.0% and 20.0% for participants randomized to CEE-alone and CEE+MPA, respectively.

Tatarchuk et al. (2024) **[13]** evaluated the safety and tolerability of ultra-low-dose estradiol and dydrogesterone (E0.5 mg/D2.5 mg) among postmenopausal women. The combination of ultra-low-dose estradiol with dydrogesterone was well tolerated among postmenopausal women, with no increase in adverse events compared to placebo. The authors analyzed 579 women who were included in the analysis of administration of 0.5 mg of 17β-estradiol and 2.5 mg of dydrogesterone (E0.5 mg/D2.5 mg, n = 288; placebo, n = 291). Women receiving E0.5 mg/D2.5 mg had greater reductions from baseline in the average daily number of hot flashes and the average daily number of moderate-to-severe hot flashes at week 4, week 8, and at the end of treatment compared with those receiving placebo. Continuous, ultra-low-dose oral administration of 0.5 mg of 17β-estradiol and 2.5 mg of dydrogesterone improved vasomotor symptoms compared with placebo in postmenopausal women, with a positive impact on health-related quality of life **[14]**.

The last positioning of the American Endocrine Society maintains that the diagnosis of androgen insufficiency in women is not well defined **[7,8]**. The Princeton Consensus in 2002 suggested a lack of motivation, fatigue, malaise, depressed mood, sexual dysfunction, decreased pubic and muscle mass, climacteric syndrome, and bone loss unresponsive to estrogen. Laboratorially, total testosterone would be <150 pg/mL, testosterone free by equilibration dialysis <1% (2 pg/mL) or S-DHEA <100 ng/mL, and testosterone dosages should be collected in the morning and in the medium of the cycle in premenopausal women **[9]**.

The Consensus itself, however, admitted that kits for androgen dosages are inappropriate for low values **[9]**. In women, these levels are often below the sensitivity of the trial, so this was a nonspecific clinical picture of difficult laboratory evidence. Both ovarian and adrenal androgens are reduced in women from the age of 25, especially early in the reproductive years. The fall is continuous with age and more precocious and marked in adrenal androgens **[15]**.

Among women aged 45 to 54 years with natural menopause, the ovary continues to secrete androgens. As the estrogen drop is about 16 times and that of androgens only two to four times, there is a relative hyperandrogenism at menopause, even with low absolute levels of androgens. In women with bilateral oophorectomy, total and free calculated testosterone levels fall significantly **[6,16]**.

Other groups of women at risk for androgen failure are those with premature ovarian failure, those on anti-androgens, oral contraceptives or oral hormone therapy (which reduce LH and increase SHBG,

decreasing free androgens), and those with adrenal insufficiency, primary or secondary to the use of corticoids or hypopituitarism **[16]**. The classical and previously established indications for prescribing testosterone in women are in the sexual sphere as a decrease in libido and sexual pleasure. Effects such as bone mass gain and increased muscle mass are also well established with the use of testosterone **[17]**.

More recently, several studies have correlated testosterone with breast cell proliferation and breast cancer. There is already a considerable amount of evidence that both testosterone and its hydrotestosterone derivative exert an inhibitory effect on the growth of the mammary cell promoted by estradiol **[1-3,18-20]**. Although progesterone has no influence on the proliferative effect of estradiol on the mammary cell, testosterone can reduce this effect by 40.0% and abolish α - α-estrogen receptor (ER-α) expression **[21]**. Several studies have concluded that androgen induces a downregulation of breast epithelial proliferation and estrogen receptor expression, suggesting that the estrogen / androgen association in menopausal hormone therapy may reduce the risk of breast cancer **[1-6]**.

No direct relationship between endogenous levels of androgens and libido has been demonstrated. The response occurred only with supraphysiological doses of testosterone, whose long-term safety is uncertain **[15]**. In women, excess androgens can lead to aesthetic repercussions such as acne, hirsutism, and even virilization. Aggression, water retention, increased blood pressure, and cardiovascular problems may occur. Laboratorially, there is a tendency to polycythemia, a decrease in HDL, and an increase in fibrinogen. Androgens increase visceral fat, free fatty acids, and impair insulin action **[9-16]**.

Hepatic damage may occur with oral formulations. There are several presentations on the use of testosterone in women. In general, injectable testosterone is not recommended because of the pharmacological nature of this route, leading to important variations in circulating levels as well as deposition of the steroid. On the other hand, the intramuscular route has been shown to be efficient in oophorectomized women **[8]**.

Low-dose methyltestosterone (1.25-2.5 mg) has been shown to be effective in relieving menopausal symptoms, bone mass, sexual function, and quality of life variables. Oral testosterone undecanoate is available in Europe and Canada and is preferably the lymphatic absorption. Testosterone implants are inserted every 4 to 6 months apart; monitoring circulating levels is critical to patient safety and should never exceed physiological levels (70-90 ng / dL) **[19]**.

Women's testosterone patches are not yet marketed in Brazil, but studies using 150 to 300 µg have been very satisfactory. The hydroalcoholic testosterone gel used for women (1 g / day) at a dose of 1/5 of the value used in men may be efficient for body composition, muscle strength, and sexual function. DHEA, although used in several studies at the dose of 50 mg / day, has only efficacy in releasing testosterone. Up to the present, it is not recommended for THM in women with preserved adrenal function **[20]**.

Major Literary Findings of the Correlation of Testosterone Use and the Cardiovascular System

Testosterone is an essential hormone for women, with physiological actions mediated directly or through aromatization to estradiol throughout the body **[5-8]**. Despite the crucial role of testosterone and the high circulating concentrations of this hormone in relation to estradiol in women, studies of its action and the effects of testosterone deficiency and replacement in women are scarce. The main indication for the prescription of testosterone for women is the loss of sexual desire, which causes substantial concern for the affected women. That no formulation has been approved for this purpose has not prevented the widespread use of testosterone by women, offlabel or as combination therapy **[9-16]**.

Observational studies indicate that testosterone has favorable cardiovascular effects measured by substitution results. However, the associations between endogenous testosterone and the risk of cardiovascular disease and total mortality, particularly in older women, have not yet been established **[17-20]**. No adverse cardiovascular effects have been observed in studies of transdermal testosterone therapy in women. Clinical trials suggest that exogenous testosterone increases cognitive performance and improves musculoskeletal health in postmenopausal women. Unmet needs include the availability of women-approved testosterone formulations and studies to elucidate the contribution of testosterone to cardiovascular, cognitive, and musculoskeletal health and cancer risk **[21]**.

Androgen levels differed substantially between women with and without ovarian dysfunction, and elevated androgen levels were associated with cardiometabolic deficiency in all women regardless of clinical condition **[22-24]**. Sexual steroid hormones play important roles in the development of cardiovascular diseases, both at high and low levels. This cross-sectional study included 680 women with polycystic ovary syndrome, premature ovarian failure, natural postmenopausal women, or regular menstrual

cycles (170 women per group) [24].

Serum testosterone, androstenedione, and dehydroepiandrosterone sulfate measurements were performed using mass spectrometry on liquid chromatography. Body mass index (BMI), blood pressure, lipid profiles, glucose, insulin, and SHBG were evaluated, and the bioactive fraction of circulating testosterone was calculated using the androgen-free index (FAI) [25]. Female PCOS women were hyperandrogenic [FAI mean 4.9 (IQR 3.6-7.4)], and POI women were hypoandrogenic [FAI = 1.2 (0.8-1.7)] compared to women RC [FAI = 1.7 (1.1-2.8)], after adjusting for age, ethnicity, smoking, and BMI (P <0.001). After adjusting for age, there were no significant differences in androgens between POI and NM (p=0.15) women and between NM and CR (p=.27), the latter indicating that chronological aging rather than aging ovary influences the differences between pre- and postmenopausal women. A high FAI was associated with high triglycerides (β log FAI for PCOS: 0.45, p<0.001, POI: 0.25, p<0.001, NM: 0.20, p= 0.002), insulin (β log FAI for PCOS: 0.77, POI: 0.44, NM: 0.40, all p<0.001), HOMA-IR (β log FAI for PCOS: 0.82, POI: 0.46, NM: all p<0.001) and mean arterial pressure (log β FAI for PCOS: 0.05, p= 0.002, POI: 0.07, p<0.001, NM: 0.04, p= 0.04) in all women . With increased glucose (β log FAI for PCOS: 0.05, p = 0.003, NM: 0.07, p<0.001) and decreased high density lipoprotein (β log FAI for PCOS: -0.23, p<0.001, NM: -0.09, p=0.03) in PCOS and NM women; And with increased low density lipoprotein (β log FAI for POI: 0.083, p= 0.041) in female POI. Adjustment for BMI attenuated the associations observed. The associations between FAI and cardiometabolic characteristics were the strongest in women with PCOS, even after adjustment for BMI [19].

The incidence of cardiovascular disease increases dramatically with age in men and women. As a woman's risk of cardiovascular disease increases markedly after the onset of menopause, there has been increasing interest in the effect of estrogen on the heart and its role in the pathophysiology of these diseases. Much less attention has been given to the impact of testosterone on the heart, even though testosterone levels also decrease with age, and low levels of testosterone are linked to the development of cardiovascular disease [20].

The knowledge that the receptors of all major sex steroid hormones, including testosterone, are present in individual cardiomyocytes suggests that these hormones can influence the heart at the cellular level. In fact, it is well established that there are male-female differences in the release and intracellular contraction of Ca (2+) in isolated ventricular myocytes. Increasing evidence suggests that these differences arise from the effects of sex steroid hormones on processes involved in intracellular homeostasis of Ca (2+). The myocardial contractile function is modified by testosterone, focusing on the impact of testosterone on processes that regulate the handling of Ca (2+) in the ventricular myocyte level. The idea that testosterone regulates Ca (2+) treatment in the heart is important, as Ca (2+) deregulation plays a key role in the pathogenesis of a variety of different cardiovascular diseases. A better understanding of the sexual hormonal regulation of myocardial homeostasis (2+) may reveal new targets for the treatment of cardiovascular disease in all older adults [20].

Androgens play a key role in cardiovascular function, and their effects differ between men and women. In postmenopausal women, the replacement of testosterone at physiological levels is associated with general well-being. However, a definitive explanation on how androgens have an impact on cardiovascular health in postmenopausal women and whether they can be used for cardiovascular treatment has not yet been established. With these objectives, a systematic review of existing studies on the relationship between androgens and cardiovascular diseases and the effects of testosterone therapy on cardiovascular outcomes in postmenopausal women was carried out [21].

The few existing studies on cardiovascular outcomes in postmenopausal women indicate no deleterious effect or effect of increased androgen and increased cardiovascular risk. However, there is evidence of a favorable effect of androgens on cardiovascular markers of substitution in postmenopausal women, such as high-density lipoprotein cholesterol, total cholesterol, body fat mass, and triglycerides. Therefore, further studies are needed to elucidate the impact of androgen therapy on cardiovascular health in postmenopausal women. The cardiovascular effect of testosterone or methyltestosterone with or without concomitant estrogens needs to be clarified [21]. The addition of testosterone to a hormone therapy regimen has beneficial effects on sexual function in postmenopausal women, and subsequent studies have supported the role of testosterone in sexual function and well-being [15].

Thirty-one postmenopausal women undergoing transdermal estradiol (E2) replacement therapy, 36 with bilateral oophorectomy (group O), and 45 controls (group C) were studied through venous occlusion plethysmography, bioimpedance, DEXA, biochemical, hormonal, and inflammatory. The total testosterone (TT) level in group O was 11.0 (4.0-17.75) vs 23.0

(10.0-42.5) ng/dL in group C (p= 0.001). Blood flow in the forearm in ml / min / 100 mL tissue was lower in group O compared to group C at baseline (1.57 (1.05-2.47) versus 2.19 (1,59-2,66) p= 0.036), after reactive hyperemia response (endothelium- dependent flow-mediated dilation, 3.44 (2.38-4.35) versus 4.3 (3.09-5.52 , p=0.031) and after nitroglycerin (independent endothelial dilatation, 1.39 (0.99-1.7) vs 1.76 (1.15-2.0), p=0.025), with a positive correlation between TT and all parameters except for the reactive hyperemia response (r = 0.233-0.312, p= 0.036-0.004). The absence of ovarian testosterone production in recent post-menopausal oophorectomized women has been associated with deleterious effects on endothelial function **[17]**.

A study demonstrated that estradiol and testosterone have a synergistic effect on early-stage atherosclerosis, and a definite appropriate E2 / T ratio replacement therapy can significantly suppress the development of atherosclerosis by reducing lipid lesions, reducing the formation of foam cells, reducing endothelial injury, modulating the function of the coagulation system, and inhibiting inflammation **[18]**.

Limitations

Further analysis of the effects of sex hormones and their receptors on vascular function should improve understanding of sex differences and menopause-related changes in vascular signaling, and provide better guidance for the management of postmenopausal cardiovascular disease.

Conclusion

It was concluded that hormone replacement therapy is a sex-specific and time-dependent primary cardiovascular disease prevention therapy that concomitantly reduces all-cause mortality as well as other aging-related diseases. Observational studies did not suggest an increased risk of myocardial infarction in postmenopausal women with diabetes prescribed HRT. Lipoprotein, LDL-C, and insulin resistance were lower with hormone therapy, and HDL-C levels were higher with hormone therapy compared to placebo. Thus, hormone therapy in women was shown to be important for improving organic functions and quality of life, as well as showing a bias in reducing cardiovascular events.

CRediT

Author contributions: **Conceptualization-** Ana Angélica Nogueira Lima, Carmen Melo do Vale; **Data curation-** Ana Angélica Nogueira Lima, Carmen Melo do Vale, Marcelo Rodrigues Zacarkim, Firmino Lucas Barreto de Matos Nobre, Lara Maria Vilaça de Figueiredo, José de Sousa Xavier, Alfredo Máximo Grilo Jardim, Ana Gabriella de Almeida Araújo, Iago Aum Malaspina, Vittor Candido Soares; **Formal Analysis-** Ana Angélica Nogueira Lima, Carmen Melo do Vale; **Investigation-**Marcelo Rodrigues Zacarkim, Firmino Lucas Barreto de Matos Nobre, Lara Maria Vilaça de Figueiredo, José de Sousa Xavier, Alfredo Máximo Grilo Jardim, Ana Gabriella de Almeida Araújo, Iago Aum Malaspina, Vittor Candido Soares; **Project administration-**Ana Angélica Nogueira Lima, Carmen Melo do Vale; **Supervision-**Ana Angélica Nogueira Lima, Carmen Melo do Vale; **Writing - original draft-**Ana Angélica Nogueira Lima, Carmen Melo do Vale, Marcelo Rodrigues Zacarkim, Firmino Lucas Barreto de Matos Nobre, Lara Maria Vilaça de Figueiredo, José de Sousa Xavier, Alfredo Máximo Grilo Jardim, Ana Gabriella de Almeida Araújo, Iago Aum Malaspina, Vittor Candido Soares; **Writing-review & editing-** Ana Angélica Nogueira Lima, Carmen Melo do Vale, Marcelo Rodrigues Zacarkim, Firmino Lucas Barreto de Matos Nobre, Lara Maria Vilaça de Figueiredo, José de Sousa Xavier, Alfredo Máximo Grilo Jardim, Ana Gabriella de Almeida Araújo, Iago Aum Malaspina, Vittor Candido Soares

Acknowledgment

Not applicable.

Ethical Approval

Not applicable.

Informed Consent

Not applicable.

Funding

Not applicable.

Data Sharing Statement

No additional data are available.

Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate®.

Application of Artificial Intelligence (AI)

Not applicable.

Peer Review Process

It was performed.

References

1. Machuca JN, Rosales-Alvarez CP. Cardiovascular Disease in Women and the Role of Hormone Replacement Therapy. Cureus. 2024 Sep 19;16(9):e69752. doi: 10.7759/cureus.69752.
2. Mukherjee A, Davis SR. Update on Menopause Hormone Therapy; Current Indications and Unanswered Questions. Clin Endocrinol (Oxf). 2025 Jan 29. doi: 10.1111/cen.15211.
3. Harper-Harrison G, Carlson K, Shanahan MM. Hormone Replacement Therapy. 2024 Oct 6. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–. PMID: 29630243.
4. Xia W, Khalil RA. Hormone Replacement Therapy and Cardiovascular Health in Postmenopausal Women. Int J Mol Sci. 2025 May 24;26(11):5078. doi: 10.3390/ijms26115078.
5. Rosano GM, Spoletini I , Vitale C . Cardiovascular disease in women, is it different to men? The role of sex hormones. Climacteric. 2017; Apr;20(2):125-128. doi: 10.1080/13697137.2017.1291780. Epub 2017 Mar 2.
6. Mikkola TS , Savolainen-Peltonen H , Venetkoski M , Ylikorkala O .New evidence for cardiac benefit of postmenopausal hormonetherapy. Climacteric. 2017 Feb;20(1):5-10. doi: 10.1080/13697137.2016.1262839. Epub 2017 Jan 2.
7. "The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. Menopause. 2022 Jul 1;29(7):767-794. doi: 10.1097/GME.0000000000002028.
8. Management of osteoporosis in postmenopausal women: the 2021 position statement of The North American Menopause Society. Menopause. 2021 Sep 1;28(9):973-997. doi: 10.1097/GME.0000000000001831.
9. Davis SR, Wahlin-Jacobsen S. Testosterone in women--the clinical significance. Lancet Diabetes Endocrinol. 2015 Dec;3(12):980-92. doi: 10.1016/S2213-8587(15)00284-3.
10. Hodis HN, Mack WJ. Menopausal Hormone Replacement Therapy and Reduction of All-Cause Mortality and Cardiovascular Disease: It Is About Time and Timing. Cancer J. 2022 May-Jun 01;28(3):208-223. doi: 10.1097/PPO.0000000000000591.
11. Risni HW, Khan A, Insani WN, Wei L, Brauer R. Cardiovascular risk of hormone replacement therapy in menopausal women with diabetes: a systematic review and meta-analysis of clinical trials and observational studies. Expert Opin Pharmacother. 2024 Oct;25(15):2089-2105. doi: 10.1080/14656566.2024.2411442.
12. Nudy M, Aragaki AK, Jiang X, Manson JE, Shadyab AH, Jung SY, Martin LW, Wild RA, Womack C, Mouton CP, Rossouw JE, Schnatz PF. Long-Term Changes to Cardiovascular Biomarkers After Hormone Therapy in the Women's Health Initiative Hormone Therapy Clinical Trials. Obstet Gynecol. 2025 Apr 1;145(4):357-367. doi: 10.1097/AOG.0000000000005862.
13. Tatarchuk T, Stevenson JC, Yu Q, Kahler E, Graziano Custodio M, Ren M, Nappi RE, Karpova V, Simoncini T. Ultra-low-dose continuous combined estradiol and dydrogesterone in postmenopausal women: A pooled safety and tolerability analysis. Gynecol Endocrinol. 2024 Dec;40(1):2375577. doi: 10.1080/09513590.2024.2375577.
14. Yu Q, Stevenson JC, Tatarchuk T, Nappi RE, Graziano Custodio M, Kahler E, Simoncini T, Yang J, Ren M. Ultra-low-dose estradiol and dydrogesterone for treatment of vasomotor symptoms in Europe and China. Climacteric. 2024 Oct;27(5):494-500. doi: 10.1080/13697137.2024.2380364.
15. Ann Drillich, Susan R. Davis. Androgen therapy in women: What we think we know. Experimental Gerontology 42 (2007) 457–462.
16. Pardini D. Hormone replacement therapy in menopause. Arq Bras Endocrinol Metab. 2014;58/2.
17. Rech CM, Clapauch R, de Souza Md, Bouskela E. Low testosterone levels are associated with endothelial dysfunction in oophorectomized early postmenopausal women. Eur J Endocrinol. 2016 Mar;174(3):297-306.
18. Dai W, Ming W, Li Y, Zheng HY, Wei CD, Rui Z, Yan C. Synergistic Effect of a Physiological Ratio of Estradiol and Testosterone in the Treatment of Early-stage Atherosclerosis. Arch Med Res. 2015 Nov;46(8):619-29. doi: 10.1016/j.arcmed.2015.11.003.
19. Daan NMP, Jaspers L, Koster MPH, Broekmans FJM, Rijke YB, Franco OH, Laven JSE, Kavousi

M, Fauser BCJM. Androgen levels in women with various forms of ovarian dysfunction: associations with cardiometabolic features. Human Reproduction, 2015, vol.30, No.10 pp. 2376–2386.

20. Ayaz O, Howlett SE. Testosterone modulates cardiac contraction and calcium homeostasis: cellular and molecular mechanisms. Biol Sex Differ. 2015 Apr 29;6:9. doi: 10.1186/s13293-015-0027-9.
21. Xie W, Ren M, Li L, Zhu Y, Chu Z, Zhu Z, Ruan Q, Lou W, Zhang H, Han Z, Huang X, Xiang W, Wang T, Yao P. Perinatal testosterone exposure potentiates vascular dysfunction by ERβ suppression in endothelial progenitor cells. PLoS One. 2017 Aug 15;12(8):e0182945. doi: 10.1371/journal.pone.0182945.
22. Spoletini I, Vitale C, Pelliccia F, Fossati C, Rosano GM. Androgens and cardiovascular disease in postmenopausal women: a systematic review. Climacteric. 2014 Dec;17(6):625-34.
23. Casanova G, Bossardi RR, Ziegelmann P, Spritzer PM. Effects of low-dose versus placebo or conventional-dose postmenopausal hormone therapy on variables related to cardiovascular risk: a systematic review and meta-analyses of randomized clinical trials, J. Clin. Endocrinol. Metab. 2015, 100:1028-1037.
24. Kotani K, Sahebkar A, Serban C, Andrica F, Toth PP, Jones SR, et al. Lipid and blood pressure meta-analysis collaboration (LBPMC) group tibolone decreases lipoprotein(a) levels in postmenopausal women: a systematic review and meta-analysis of 12 studies with 1009 patients. Atherosclerosis. 2015, 242:87-96.
25. Anagnostis P, Stevenson JC, CrooK D, Johnston DG, Godsland IF. Effects of menopause, sex and age on lipids and high-density lipoprotein cholesterol subfractions, Maturitas 81 (2015) 62-68.