

ARTÍCULO ESPECIAL

# The Influence of Sex Hormones on Cardiovascular Health: Current Perspectives and Future Directions

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## ABSTRACT

The intricate relationship between sex hormones and cardiovascular health has garnered increasing attention, revealing significant implications for both disease prevention and therapeutic strategies. This literature review aims to elucidate the multifaceted roles of estrogen, progesterone, and testosterone in cardiovascular physiology and pathology. Estrogen is widely recognized for its protective effects on vascular function, lipid metabolism, and atherosclerosis prevention, while testosterone presents a more complex picture with both beneficial and detrimental impacts on cardiovascular risk. Progesterone, often overlooked, also plays a critical role in modulating these effects. Additionally, this review explores how sex hormones influence endothelial function, inflammatory responses, and contribute to gender differences in cardiovascular disease prevalence. The impact of menopause and hormone replacement therapy (HRT) on cardiovascular health is critically examined, highlighting ongoing debates and current guidelines. Furthermore, the cardiovascular implications of gender-affirming hormone therapy in transgender individuals are discussed. By synthesizing current perspectives, incorporating recent studies up to 2023, and identifying future research directions, this review underscores the potential for personalized medicine approaches that consider genetic, environmental, and lifestyle factors, as well as healthcare equity, to optimize cardiovascular health outcomes.

# La influencia de las hormonas sexuales en la salud cardiovascular: perspectivas actuales y direcciones futuras

**Palabras clave:**

*Hormonas sexuales, Salud cardiovascular, Estrógeno, Testosterona, Terapia de reemplazo hormonal, Medicina personalizada, Equidad en la atención médica (Fuente: DeCS - BIREME).*

## RESUMEN

La intrincada relación entre las hormonas sexuales y la salud cardiovascular ha atraído cada vez más atención, revelando implicaciones significativas tanto para la prevención de enfermedades como para las estrategias terapéuticas. Esta revisión de la literatura tiene como objetivo dilucidar las funciones multifacéticas de los estrógenos, la progesterona y la testosterona en la fisiología y patología cardiovascular. El estrógeno es ampliamente reconocido por sus efectos protectores sobre la función vascular, el metabolismo de los lípidos y la prevención de la aterosclerosis, mientras que la testosterona presenta un cuadro más complejo con impactos tanto beneficiosos como perjudiciales sobre el riesgo cardiovascular. La progesterona, que a menudo se pasa por alto, también desempeña un papel fundamental en la modulación de estos efectos. Además, esta revisión explora cómo las hormonas sexuales influyen en la función endotelial, las respuestas inflamatorias y contribuyen a las diferencias de género en la prevalencia de enfermedades cardiovasculares. Se examina críticamente el impacto de la menopausia y la terapia de reemplazo hormonal (TRH) en la salud cardiovascular, destacando los debates en curso y las pautas actuales. Además, se discuten las implicaciones cardiovasculares de la terapia hormonal de afirmación del género en personas transgénero. Al sintetizar las perspectivas actuales, incorporar estudios recientes hasta 2023 e identificar futuras direcciones de investigación, esta revisión subraya el potencial de los enfoques de medicina personalizada que consideran factores genéticos, ambientales y de estilo de vida, así como la equidad en la atención médica, para optimizar los resultados de salud cardiovascular.

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## INTRODUCTION

Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality worldwide, posing a significant public health challenge <sup>(1)</sup>. While traditional risk factors such as hypertension, dyslipidemia, and smoking are well-established, emerging evidence suggests that sex hormones play a crucial role in modulating cardiovascular health <sup>(2)</sup>. Estrogen, progesterone, and testosterone, traditionally associated with reproductive functions, exert diverse effects on the cardiovascular system <sup>(3)</sup>. Understanding the intricate interplay between these hormones and cardiovascular physiology is essential for elucidating sex disparities in CVD incidence, presentation, and outcomes <sup>(4)</sup>.

Estrogen, primarily synthesized in the ovaries, exerts vasoprotective effects by promoting endothelial nitric oxide synthase (eNOS) expression and enhancing endothelial function, which involves the regulation of vascular tone, blood flow, and the balance between coagulation and fibrinolysis <sup>(5)</sup>. Experimental studies have demonstrated estrogen's ability to attenuate vascular inflammation, inhibit smooth muscle cell proliferation, and enhance high-density lipoprotein (HDL) cholesterol levels, collectively reducing atherosclerotic burden <sup>(6)</sup>. Moreover, estrogen receptors are expressed in various cardiovascular tissues, suggesting direct cardioprotective mechanisms independent of its effects on lipid metabolism and blood pressure regulation <sup>(7)</sup>.

In contrast, testosterone, predominantly produced in the testes, exhibits divergent effects on cardiovascular risk. While testosterone may confer cardioprotective benefits by improving insulin sensitivity, enhancing skeletal muscle mass, and reducing visceral adiposity <sup>(8,9)</sup>, it is also implicated in promoting proatherogenic processes such as endothelial dysfunction, arterial stiffness, and thrombosis <sup>(10,11)</sup>. The complex relationship between testosterone and cardiovascular health underscores the importance of considering sex-specific effects and hormone balance in disease risk assessment and management.

Progesterone, often overshadowed by estrogen and testosterone, exerts regulatory effects on vascular tone, inflammation, and thrombosis <sup>(12)</sup>. Progesterone receptors are expressed in endothelial cells, smooth muscle cells, and cardiomyocytes, suggesting a direct influence on cardiovascular function <sup>(13)</sup>. Emerging evidence suggests a potential role for progesterone in modulating the cardiovascular effects of estrogen and testosterone, highlighting its significance in sex hormone-mediated cardioprotection.

Despite advances in our understanding of sex hormone-mediated cardiovascular effects, several

challenges remain. Menopause, characterized by declining estrogen levels, is associated with an increased risk of CVD, prompting debates regarding the cardiovascular safety and efficacy of hormone replacement therapy (HRT) <sup>(14,15)</sup>. Furthermore, the cardiovascular implications of gender-affirming hormone therapy in transgender individuals warrant further investigation to optimize risk assessment and management strategies <sup>(16)</sup>.

In this literature review, we aim to provide a comprehensive overview of the current perspectives on the influence of sex hormones on cardiovascular health. By synthesizing existing evidence, incorporating recent studies up to 2023, and identifying future research directions, we seek to enhance our understanding of sex-specific cardiovascular risk factors and facilitate the development of personalized therapeutic approaches that consider genetic, environmental, and lifestyle factors, as well as addressing healthcare disparities.



## DEVELOPMENT

### Estrogen and cardiovascular protection

Estrogen, a pivotal sex hormone primarily synthesized in the ovaries, plays a critical role in cardiovascular physiology, exerting multifaceted effects that contribute to its protective role against cardiovascular diseases <sup>(17)</sup>. Mechanistically, estrogen influences various aspects of vascular function, lipid metabolism, blood pressure regulation, and atherosclerosis development. These effects are mediated through both genomic and non-genomic mechanisms, involving estrogen receptors abundantly expressed in cardiovascular tissues <sup>(18)</sup>. Activation of estrogen receptors leads to the regulation of gene transcription, resulting in downstream effects on vascular homeostasis, inflammation, and oxidative stress. Additionally, estrogen exerts rapid, non-genomic effects via membrane-bound estrogen receptors, activating signaling pathways such as PI3K/Akt and MAPK/ERK, which modulate endothelial function and vascular tone.

One of the key mechanisms underlying estrogen's cardiovascular protection is its ability to promote endothelial function. Estrogen enhances endothelial nitric oxide synthase (eNOS) expression and activity, leading to increased nitric oxide (NO) production <sup>(19)</sup>. NO, a potent vasodilator, regulates vascular tone, inhibits platelet aggregation, and prevents smooth muscle cell proliferation, thereby maintaining vascular homeostasis and preventing atherosclerosis <sup>(20)</sup>. Furthermore, estrogen attenuates endothelial dysfunction by inhibiting endothelin-1 production, reducing oxidative stress, and modulating endothelial progenitor cell function.

Estrogen also plays a crucial role in lipid metabolism, exerting favorable effects on lipoprotein profiles. It increases high-density lipoprotein cholesterol (HDL-C) levels while reducing low-density lipoprotein cholesterol (LDL-C) and triglycerides<sup>(21)</sup>. Estrogen promotes reverse cholesterol transport by upregulating ATP-binding cassette transporters, facilitating cholesterol efflux from macrophages and promoting its transport to the liver for excretion. Moreover, estrogen inhibits the expression of proinflammatory cytokines and adhesion molecules, thereby attenuating lipid oxidation, inflammation, and atherosclerotic plaque formation<sup>(22)</sup>.

In terms of blood pressure regulation, estrogen exhibits complex effects, demonstrating both vasodilatory and antihypertensive properties<sup>(23)</sup>. It enhances endothelial-dependent vasodilation, inhibits the renin-angiotensin-aldosterone system, and modulates sympathetic nervous system activity, collectively contributing to blood pressure homeostasis. Furthermore, estrogen inhibits vascular smooth muscle cell proliferation and migration, reducing neointimal hyperplasia and attenuating atherosclerotic lesion formation<sup>(24)</sup>.

The comprehensive understanding of estrogen's multifaceted effects on cardiovascular physiology provides insights into its potential therapeutic implications for cardiovascular diseases. However, further elucidation of the underlying mechanisms and clinical translation of these findings are essential for the development of targeted therapeutic strategies to mitigate cardiovascular risk.

### Testosterone and cardiovascular risk

Testosterone, primarily synthesized in the testes, significantly influences cardiovascular physiology and pathology, extending beyond its classical roles in male reproductive functions and musculoskeletal development<sup>(25)</sup>. Its actions are mediated through androgen receptors expressed in cardiovascular tissues, modulating gene transcription and intracellular signaling pathways. Consequently, testosterone's effects encompass various cardiovascular parameters, including blood pressure regulation, lipid metabolism, inflammation, and vascular function.

Epidemiological studies have unveiled associations between testosterone levels and cardiovascular diseases (CVD) in both sexes. In men, low testosterone levels correlate with an elevated risk of coronary artery disease (CAD), myocardial infarction (MI), and heart failure. Conversely, in women, conditions characterized by androgen excess, such as polycystic ovary syndrome (PCOS), often exhibit adverse cardiovascular outcomes, including hypertension, dyslipidemia, and atherosclerosis<sup>(26)</sup>.

Testosterone's impact on lipid metabolism is profound, influencing cholesterol synthesis, transport, and metabolism. Testosterone deficiency in men is linked to unfavorable lipid profiles, typified by decreased high-density lipoprotein cholesterol (HDL-C) levels and elevated low-density lipoprotein cholesterol (LDL-C) levels<sup>(27)</sup>. Conversely, women with PCOS frequently experience dyslipidemia and insulin resistance alongside androgen excess, contributing to an increased risk of metabolic syndrome.

Understanding the interplay between testosterone and cardiovascular health is crucial for risk stratification and targeted interventions. While testosterone deficiency in men underscores an elevated CVD risk, androgen excess in women, particularly in conditions like PCOS, presents unique challenges in cardiovascular risk management. Thus, elucidating the mechanistic underpinnings of testosterone-mediated cardiovascular effects holds promise for tailored therapeutic strategies aimed at mitigating cardiovascular risk in individuals with hormonal imbalances.

### Progesterone and cardiovascular health

Progesterone, a key sex hormone primarily produced in the ovaries, plays a crucial role in reproductive physiology and has emerging implications in cardiovascular health<sup>(28)</sup>. While traditionally recognized for its role in regulating the menstrual cycle and supporting pregnancy, progesterone exerts diverse effects on the cardiovascular system, interacting intricately with estrogen to modulate vascular function, inflammation, and thrombosis.

Progesterone influences various aspects of cardiovascular physiology, including vascular tone, endothelial function, and coagulation. Progesterone receptors are expressed in vascular tissues, suggesting direct effects on vascular smooth muscle cells and endothelial cells<sup>(29)</sup>. Progesterone promotes vasodilation by enhancing nitric oxide (NO) bioavailability and modulating endothelial-derived factors, contributing to the maintenance of vascular homeostasis<sup>(30)</sup>. Moreover, progesterone exhibits antithrombotic properties by inhibiting platelet aggregation and thromboxane A2 synthesis, thereby attenuating thrombotic risk.

Progesterone interacts dynamically with estrogen to modulate cardiovascular function. While estrogen primarily exerts vasodilatory effects, progesterone may counterbalance estrogen-induced vasodilation by promoting vasoconstriction through its effects on vascular smooth muscle tone<sup>(31)</sup>. Furthermore, progesterone regulates estrogen receptor expression and activity, influencing estrogen-mediated effects on lipid metabolism, inflammation, and atherosclerosis.

sis. The intricate interplay between progesterone and estrogen underscores the complexity of sex hormone regulation in cardiovascular health and disease.

The overall effects of progesterone on cardiovascular health remain complex and context-dependent. While some studies suggest beneficial effects, such as vasodilation and anti-inflammatory actions, others have implicated progesterone in adverse cardiovascular outcomes, particularly in the context of hormone replacement therapy<sup>(32,33)</sup>. Furthermore, the effects of progesterone may vary based on factors such as dose, duration of exposure, and the presence of coexisting cardiovascular risk factors<sup>(34)</sup>. Thus, further research is warranted to elucidate the specific mechanisms underlying progesterone's cardiovascular effects and its clinical implications for cardiovascular risk stratification and management.

### Sex hormones and endothelial function

Sex hormones, including estrogen and testosterone, exert profound effects on endothelial function, playing pivotal roles in regulating vascular homeostasis and cardiovascular health<sup>(35)</sup>. Endothelial cells, lining the inner surface of blood vessels, serve as key regulators of vascular tone, inflammation, and thrombosis, and they actively respond to hormonal cues. Both estrogen and testosterone influence endothelial function through intricate mechanisms involving modulation of nitric oxide (NO) production, oxidative stress, and vascular tone regulation<sup>(36)</sup>.

Estrogen, primarily synthesized in the ovaries, exerts vasoprotective effects on endothelial cells, promoting vasodilation and inhibiting vascular inflammation and thrombosis<sup>(37)</sup>. Estrogen receptors, including estrogen receptor alpha (ER $\alpha$ ) and estrogen receptor beta (ER $\beta$ ), are expressed in endothelial cells, enabling direct genomic and non-genomic actions of estrogen<sup>(38)</sup>. Estrogen enhances endothelial NO synthase (eNOS) expression and activity, leading to increased NO production, a critical mediator of vasodilation and vascular homeostasis. Additionally, estrogen suppresses the expression of adhesion molecules and proinflammatory cytokines in endothelial cells, thereby attenuating endothelial dysfunction and atherosclerosis.

Conversely, testosterone, predominantly synthesized in the testes, exhibits complex effects on endothelial function, demonstrating both vasodilatory and vasoconstrictive actions. Testosterone receptors, including androgen receptors, are expressed in endothelial cells, modulating intracellular signaling pathways involved in NO production and vascular tone regulation<sup>(39)</sup>. Testosterone enhances eNOS expression and NO production in endothelial cells under physiological conditions, promoting

vasodilation and maintaining vascular homeostasis. However, in pathological states characterized by androgen excess or imbalance, testosterone may exert detrimental effects on endothelial function, contributing to endothelial dysfunction and cardiovascular risk<sup>(40)</sup>.

The intricate interplay between estrogen and testosterone further influences endothelial function and vascular tone regulation. Estrogen and testosterone may exert opposing effects on endothelial NO production and vascular tone, highlighting the importance of sex hormone balance in cardiovascular health<sup>(41)</sup>. Moreover, the effects of sex hormones on endothelial function may vary based on factors such as hormone levels, receptor expression, and the presence of coexisting cardiovascular risk factors. Understanding the complex interactions between sex hormones and endothelial function is essential for elucidating their roles in cardiovascular physiology and disease pathogenesis.

### Menopause, hormone replacement therapy, and cardiovascular health

Menopause represents a critical transition in a woman's life characterized by the cessation of ovarian function and a decline in sex hormone production, particularly estrogen and progesterone. This hormonal shift is associated with significant changes in cardiovascular risk factors, including alterations in lipid metabolism, vascular function, and inflammation, culminating in an increased risk of cardiovascular disease (CVD) post-menopause.

Hormone replacement therapy (HRT) has long been advocated as a potential intervention to mitigate the adverse cardiovascular effects associated with menopause [42]. Estrogen-based HRT, either alone or in combination with progestogens, aims to alleviate menopausal symptoms and preserve bone health while potentially conferring cardiovascular benefits. Estrogen replacement therapy has been shown to improve lipid profiles, promote vasodilation, and attenuate endothelial dysfunction, all of which contribute to a favorable cardiovascular risk profile<sup>(42,43)</sup>.

However, the cardiovascular benefits of HRT remain the subject of debate, with conflicting evidence from observational studies and randomized controlled trials (RCTs). While observational studies have suggested a protective effect of HRT against CVD, RCTs such as the Women's Health Initiative (WHI) have reported an increased risk of cardiovascular events, including myocardial infarction, stroke, and venous thromboembolism, particularly with the use of estrogen plus progestin therapy<sup>(44)</sup>.



Current guidelines recommend individualized decision-making regarding the initiation of HRT for menopausal symptom management, taking into account factors such as age, menopausal status, cardiovascular risk profile, and personal preferences<sup>(45)</sup>. HRT initiation should be accompanied by a thorough assessment of cardiovascular risk factors, including lipid levels, blood pressure, and family history of CVD<sup>(46)</sup>. Furthermore, HRT should be prescribed at the lowest effective dose for the shortest duration necessary to achieve treatment goals, with regular reevaluation of the benefits and risks.

Despite the controversies surrounding HRT, it remains a valuable therapeutic option for select menopausal women, particularly those experiencing severe menopausal symptoms and at low cardiovascular risk. Ongoing research efforts aim to elucidate the underlying mechanisms of HRT-related cardiovascular effects and identify subgroups of women who may derive the greatest benefit from HRT while minimizing potential risks<sup>(47)</sup>.

### Sex hormones and inflammation

Sex hormones play intricate roles in modulating inflammatory responses, exerting both pro- and anti-inflammatory effects that have significant implications for cardiovascular health<sup>(48)</sup>. Estrogen, primarily synthesized in the ovaries, demonstrates anti-inflammatory properties by attenuating the production of proinflammatory cytokines and chemokines and enhancing the activity of anti-inflammatory mediators<sup>(49)</sup>. Estrogen receptors, including estrogen receptor alpha (ER $\alpha$ ) and estrogen receptor beta (ER $\beta$ ), are expressed in immune cells, allowing direct modulation of immune responses by estrogen. Estrogen suppresses the activation of nuclear factor-kappa B (NF- $\kappa$ B) and mitogen-activated protein kinase (MAPK) signaling pathways, thereby inhibiting the expression of proinflammatory genes and mitigating inflammatory responses.

Conversely, testosterone, predominantly synthesized in the testes, exhibits complex effects on inflammation, demonstrating both pro- and anti-inflammatory properties depending on the context and target tissue<sup>(50)</sup>. Testosterone modulates immune cell function by regulating cytokine production, phagocytosis, and T-cell proliferation, thereby influencing the balance between inflammatory and anti-inflammatory responses. Testosterone's effects on inflammation are mediated through androgen receptors expressed in immune cells, including monocytes, macrophages, and lymphocytes<sup>(51)</sup>. Testosterone may exert anti-inflammatory effects by inhibiting the production of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF- $\alpha$ ) and interleukin-6 (IL-6), while

also promoting the secretion of anti-inflammatory cytokines such as interleukin-10 (IL-10).

The dysregulation of sex hormone-mediated inflammatory responses has been implicated in the pathogenesis of chronic inflammatory conditions, including atherosclerosis and cardiovascular disease (CVD)<sup>(52)</sup>. Postmenopausal women, characterized by declining estrogen levels, exhibit a proinflammatory phenotype associated with increased circulating levels of proinflammatory cytokines and acute-phase proteins. Conversely, conditions characterized by androgen excess, such as polycystic ovary syndrome (PCOS), are associated with chronic low-grade inflammation and an increased risk of cardiovascular complications.

Understanding the complex interplay between sex hormones and inflammation is essential for unraveling the mechanisms underlying cardiovascular disease pathogenesis and identifying potential therapeutic targets. In the subsequent section, we will explore the interconnections between sex hormones, inflammation, and vascular dysfunction, further elucidating their roles in cardiovascular health and disease.

### Gender differences in cardiovascular disease

Cardiovascular disease (CVD) exhibits striking differences between men and women in terms of epidemiology, pathophysiology, and clinical presentation<sup>(53)</sup>. Historically, CVD has been considered predominantly a male disease, leading to under-recognition and undertreatment of CVD in women. However, epidemiological studies have highlighted significant gender disparities in the prevalence, risk factors, and outcomes of CVD, emphasizing the need for gender-specific approaches to cardiovascular risk assessment and management<sup>(54)</sup>.

Men have traditionally been perceived to be at higher risk for CVD compared to women, particularly at younger ages<sup>(55)</sup>. Men tend to present with CVD at an earlier age and have a higher incidence of coronary artery disease (CAD), myocardial infarction (MI), and sudden cardiac death. The influence of sex hormones, including testosterone, on traditional cardiovascular risk factors such as hypertension, dyslipidemia, and abdominal obesity, may contribute to these disparities<sup>(56)</sup>. Testosterone has been implicated in promoting atherogenic lipid profiles, insulin resistance, and proinflammatory states, predisposing men to an increased risk of CAD.

Conversely, women typically present with CVD at older ages and often exhibit different clinical manifestations compared to men<sup>(57)</sup>. Women are more likely

to present with atypical symptoms of ischemic heart disease, such as fatigue, dyspnea, and abdominal discomfort, leading to diagnostic challenges and delays in treatment initiation. Additionally, hormonal factors, including estrogen deficiency post-menopause, play a pivotal role in the pathogenesis of CVD in women<sup>(58)</sup>. Estrogen exerts vasoprotective effects by promoting vasodilation, inhibiting vascular inflammation, and attenuating atherosclerosis, thus conferring cardiovascular benefits to premenopausal women.

The interplay between sex hormones and traditional cardiovascular risk factors further contributes to gender differences in CVD. Estrogen has been shown to modulate lipid metabolism, glucose homeostasis, and endothelial function, thereby reducing the risk of CAD in premenopausal women<sup>(59)</sup>. However, with the onset of menopause and the decline in estrogen levels, women experience an accelerated progression of atherosclerosis and an increased risk of CVD, highlighting the cardioprotective effects of estrogen.

Understanding the complex interplay between gender, sex hormones, and cardiovascular risk factors is essential for developing targeted prevention and treatment strategies for CVD. In the subsequent section, we will delve into the emerging role of sex hormone-based therapies and personalized medicine approaches in addressing gender-specific cardiovascular risk factors, further optimizing cardiovascular outcomes for both men and women.

### **Cardiovascular health in transgender individuals**

The cardiovascular health of transgender individuals is an emerging area of research that has garnered increasing attention in recent years. Gender-affirming hormone therapy (GAHT), a cornerstone of gender transition for many transgender individuals, exerts profound effects on cardiovascular risk factors and outcomes<sup>(60)</sup>. Transgender women (assigned male at birth) undergoing feminizing hormone therapy typically receive estrogen and anti-androgen medications to induce physical and physiological changes consistent with their gender identity<sup>(61)</sup>. Conversely, transgender men (assigned female at birth) undergoing masculinizing hormone therapy often receive testosterone to promote virilization and suppress feminizing characteristics.

The impact of GAHT on cardiovascular health in transgender individuals is multifaceted and influenced by various factors, including the type, dose, and duration of hormone therapy, as well as baseline cardiovascular risk factors and individual characteristics<sup>(62)</sup>. Estrogen therapy in transgender women has been associated with favorable changes in lipid profiles, including reductions in total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides, although the effects on

high-density lipoprotein cholesterol (HDL-C) are less consistent<sup>(63)</sup>. Estrogen also exerts vasoprotective effects by improving endothelial function, reducing arterial stiffness, and attenuating inflammation, potentially lowering the risk of cardiovascular events.

Conversely, testosterone therapy in transgender men has been linked to adverse changes in lipid metabolism, including increases in total cholesterol, LDL-C, and triglycerides, and decreases in HDL-C, predisposing individuals to a higher risk of atherosclerosis and cardiovascular disease. Testosterone therapy may also exacerbate other cardiovascular risk factors, such as insulin resistance, hypertension, and central adiposity, particularly in individuals predisposed to metabolic syndrome<sup>(64)</sup>.

Despite these considerations, cardiovascular risk assessment and management in transgender individuals remain challenging due to limited research and clinical guidelines specific to this population<sup>(65)</sup>. Clinicians caring for transgender patients should conduct comprehensive cardiovascular risk assessments, including evaluation of traditional risk factors, lipid profiles, blood pressure, and lifestyle factors. Shared decision-making between patients and providers is crucial in determining the appropriateness of GAHT and mitigating potential cardiovascular risks through lifestyle modifications, pharmacological interventions, and close monitoring<sup>(66)</sup>.

As research in this field continues to evolve, there is a pressing need for prospective studies to elucidate the long-term cardiovascular effects of GAHT in transgender individuals and inform evidence-based guidelines for cardiovascular risk assessment and management in this population. In the subsequent section, we will explore emerging research findings and clinical considerations regarding cardiovascular health in transgender individuals, shedding light on potential avenues for improving cardiovascular outcomes in this marginalized population.

### **Future directions and therapeutic implications**

Advancements in understanding the intricate interplay between sex hormones and cardiovascular health have paved the way for novel therapeutic interventions and personalized medicine approaches aimed at optimizing cardiovascular outcomes. Future directions in this field encompass the exploration of potential new therapies targeting sex hormone pathways, the implementation of personalized medicine approaches considering hormonal status, and the identification of key areas for future research.

One promising avenue for future research lies in the development of novel therapies that selectively target sex hormone pathways to modulate cardiovascular risk factors and outcomes. Emerging

evidence suggests that agents targeting estrogen and androgen receptors, such as selective estrogen receptor modulators (SERMs) and selective androgen receptor modulators (SARMs) hold promise for the prevention and treatment of cardiovascular diseases. These agents offer the potential for more targeted and precise modulation of sex hormone signaling pathways, minimizing off-target effects and optimizing therapeutic efficacy.

Furthermore, personalized medicine approaches that take into account an individual's hormonal status and cardiovascular risk profile are poised to revolutionize cardiovascular care. Tailoring treatment strategies based on the specific hormonal milieu and cardiovascular risk factors of each patient can enhance the effectiveness of interventions and improve clinical outcomes. Biomarkers indicative of sex hormone levels, vascular function, and inflammation may serve as valuable tools for risk stratification and treatment selection, enabling clinicians to deliver more personalized and precise care to transgender individuals and patients with hormone-related cardiovascular disorders.

In addition to therapeutic interventions, future research efforts should focus on elucidating unanswered questions and addressing knowledge gaps in the field of sex hormones and cardiovascular health. Longitudinal studies are needed to investigate the long-term cardiovascular effects of gender-affirming hormone therapy in transgender individuals, including the impact on cardiovascular events, mortality, and quality of life. Furthermore, mechanistic studies exploring the underlying pathways through which sex hormones influence cardiovascular physiology and pathophysiology are essential for identifying novel therapeutic targets and developing targeted interventions.

Overall, the integration of innovative therapeutic approaches, personalized medicine strategies, and rigorous research endeavors holds immense promise for advancing our understanding of the complex interplay between sex hormones and cardiovascular health, ultimately leading to improved outcomes for individuals at risk for or affected by hormone-related cardiovascular disorders.

### Conclusions

In conclusion, the intricate interplay between sex hormones and cardiovascular health underscores the importance of tailored approaches to risk assessment, management, and therapeutic interventions. While significant strides have been made in elucidating the mechanisms underlying hormonal influences on cardiovascular physiology, numerous opportunities for further research and clinical innovation remain.

Moving forward, the integration of personalized medicine strategies, novel therapeutic modalities targeting sex hormone pathways, and rigorous longitudinal studies are essential for optimizing cardiovascular outcomes in diverse populations, including transgender individuals and those affected by hormone-related cardiovascular disorders. By advancing our understanding of these complex interactions, we can strive towards more effective prevention, treatment, and management of cardiovascular diseases, ultimately enhancing the health and well-being of individuals across the gender spectrum.



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