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Cardiovascular Implications of Gender-Affirming Hormone Treatment in the Transgender Population

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Abstract

Transgender men and women represent a growing population in the United States and Europe, with 0.5% of adults and 3% of youth identifying as transgender. Globally, an estimated 0.3-0.5% of the population identify as transgender. Despite the increasing percentage of individuals whose gender identity, gender expression and behavior differ from their assigned sex at birth, health outcomes in transgenders have been understudied. Many transgender people seek treatment with cross-sex hormone therapy starting from a young age and frequently at high doses in order to obtain the secondary sex characteristics of the desired gender. There is a need to understand the potential long-term health consequences of cross-sex hormone therapy, given that cardiovascular disease is the leading disease-specific cause of death in this population. This review discusses the cardiovascular risks of gender-affirming hormone treatments with respect to transgender women and transgender men.

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Contributors

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Chrisandra Shufelt contributed to conceptualization, funding acquisition, investigation, methodology, project administration, resources, supervision, writing the original draft, and review and editing of the manuscript.

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The authors declare that they have no conflict of interest.

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Keywords

transgender; cardiovascular disease; cross-sex hormone therapy; gender transition

Introduction

Cardiovascular disease (CVD) is the leading disease-specific cause of death for transgender people undergoing gender affirming treatment, with only suicide claiming more lives as the leader of all cause mortality.[1] However, for transgender women, the risk of death from CVD is 3-fold higher than for all other groups[2,3] Transgender is a term for people whose gender identity, gender expression and behavior do not conform to what is associated with the sex they were assigned at birth, whereas cisgender is a term for those identifying with the assigned sex at birth. For example, a transgender woman is someone whose sex was assigned as “male” at birth by virtue of their possessing male genital anatomy and male chromosomes, but later, when they can talk and express themselves, identifies as a girl/woman. Similarly, a transgender man was assigned “female” at birth because they were born with female genitalia and female chromosomes but identifies as a boy/man. Alternatively, some people’s gender identity does not fall into *either* of these binary gender norms (i.e. man or woman). Often termed “gender non-binary”, many such people use the pronouns “they/them”.[4]

Many, though not all, transgender people seek treatment for gender dysphoria, defined as distress due to the conflict between their assigned sex and the gender by which they identify.[5] The three core treatment domains for gender dysphoria are: behavioral or cognitive therapy; cross sex hormone therapy (CSHT); and body modification with gender affirming surgery. Studies have found that lack of CSHT use in those desiring physical change is a strong predictor of emotional disorders such as anxiety and depression.[6] While there are many options for gender-affirming hormone treatment, the levels of CSHT necessary to achieve physical change comes with specific implications and risks related to CVD. This review will discuss the CVD risks of gender-affirming hormone treatments with respect to transgender women and transgender men.

Methods

Authors performed a complete literature review using Pubmed for relevant articles and their reference lists. Search terms included key words such as transgender, hormone therapy, cross sex hormone therapy, estrogen, anti-androgen, progesterone, testosterone, gender affirming, cardiovascular disease, and risk factors. Inclusion criteria consisted of recency in publication date for current and accurate terminology and statistics.

Transgender Women: Feminizing Hormone Therapy

In those born anatomically female, estrogen is considered a critical and primary sex hormone. Three types of estrogens are produced endogenously during different periods of a woman’s life: estradiol, estrone, and estriol. Estradiol (E2) is the most potent and abundant sex hormone, predominantly produced by the ovary’s granulosa cells from puberty to the

onset of menopause. Depending on the stage of the menstrual cycle, E2 levels can range from 15-350 pg/mL.[7] E2 is also produced by other tissues and in men but in significantly smaller amounts of approximately 10-40 pg/mL.[7] Estrogen is responsible for developing secondary sexual characteristics such as vocal pitch, breasts, expansion of the hips, and fat deposit patterns specific to woman such as hip and gluteal regions.[8] Reproductive organs and tissues are also developed and maintained by E2 throughout puberty, adulthood, and pregnancy.

Another primary sex hormone in cisgender women is progestogen. Studies on animal models have shown that progesterone plays a role in mammary gland and breast tissue development via progesterone receptors on mammary epithelium.[9] Additionally, progesterone and estrogen work together to regulate a woman's menstrual cycle. Furthermore, there is evidence suggesting progesterone influences libido and sexual-attitudes with one study finding that progesterone reduced sexual motivation and increased same-sex mating preference.[10]

For many transgender people, gender transition includes CSHT. Transgender women who are on CSHT will often use a combination of the following classes: estrogens, antiandrogens, and progestogens. The goals for treatment include maintaining physiologic levels of estrogen both to develop secondary sex characteristics of a woman and block sex hormones to minimize secondary sex characteristics of a man. Most patients on CSHT report increased sense of well-being and decreased anxiety and depression.[6,11] Estrogen can be given as oral E2 (1-8 mg/day), transdermal E2 (50 mcg- 400 mcg frequency dependent on brand), and intramuscular E2 valerate (up to 40 mg) or cypionate (2-5mg) every other week or divided and given weekly.[12] Serum estrogen levels are recommended to be tested every 3-6 months for the first two years and then annually to ensure they are within range of a woman. Ideally, estrogen will fall in the range of 100 pg/mL to 300 pg/mL and not exceed 400 pg/mL[12] (see Table 1).

Also critical in feminizing CSHT is the suppression of endogenous testosterone with antiandrogens to reduce secondary sex characteristics of a man. Gonadotropin releasing hormone stimulates the pituitary to release luteinizing hormone which in turn stimulates the Leydig cells in the testes to produce testosterone. Antiandrogen medications drastically decrease testosterone production in the testes via blocking the hypothalamic-pituitary-adrenal axis. Oral cyproterone acetate (50-100mg/day, available in Europe) and spironolactone (50-400 mg/day) are the most commonly used antiandrogens. Similar to estrogen, serum testosterone levels should be measured at 3, 6, and 12 months for the first year and then as needed.[12] After 6 months, testosterone should drop below 55 ng/dl, though this does not always occur in all patients. In addition to its antiandrogen affects, cyproterone acetate also has antigonadotropin affects. In a 2003 European study, transdermal E2 administered with cyproterone acetate reduced testosterone levels to less than 30 ng/dL in transgender woman.[13] However, decisions regarding which CSHT to use are largely based off national regulations and reimbursement with cyproterone acetate currently not approved for use in the United States.[14]

Orchiectomy is a surgical approach whose benefits to patents include reducing testosterone to castrate levels, and, allowing the discontinuation of antiandrogens, as only trace amounts of testosterone are made by the adrenal glands.[4] According to a national transgender discrimination survey conducted in 2008, approximately 21% of 7000 transgender respondents have had an orchiectomy and 59% desired to have the surgery at some point in the future.[15] These numbers are likely lower than what would currently be expected as gender affirming surgery is covered by most commercial, Federal or State health insurance plans.

There is no evidence-based data to confirm that progesterone therapy has physical feminizing effects for transgender women.[16] However, many patients still request it based on anecdotal evidence of improved breast development, mood, and libido. The most common prescriptions are medroxyprogesterone (2.5-10 mg/day) and micronized progesterone (100-200 mg/day).

Impact of Estrogen on Cardiovascular Risk Factors

Estrogen has a profound effect on blood lipoproteins. Cisgender women taking oral contraceptive pills (OCPs) have shown increases in total cholesterol, high density lipoprotein cholesterol (HDL-C) as well as increases in low density lipoprotein cholesterol (LDL-C) and triglycerides.[17] Synthetic ethinyl estradiol used in OCPs are up to 5-10 times than menopausal hormone therapy due to the need to inhibit the hypothalamic-pituitary-ovarian axis to prevent ovulation. Therefore the amount of lipid alteration depends on the dose and route of delivery, as transdermal hormone therapy has little to no impact on cholesterol by avoiding first pass metabolism in the liver as compared with oral hormone therapy.[18] Additionally, lower doses of hormone therapy may be used to achieve similar secondary sex characteristics with transdermal routes without impacting cholesterol. In a 2016 systematic review and meta-analysis of 29 studies, transgender women on oral estrogen-based treatment had significantly increased triglyceride levels (mean 31.9 mg/dL, 95% CI 3.9-59.9) at 24 months.[19] Notably, transgender women on transdermal estrogen-based therapy experienced decreased serum triglyceride levels.[19]

Hypertension has been linked to hormone therapy use in postmenopausal women. Results from the Women’s Health Initiative showed that doses of conjugated equine estrogen (0.625 mg/day) and conjugated equine estrogen plus medroxyprogesterone acetate (2.5 mg/day) had an incident rate 18% higher than placebo.[20] However, in the transgender women, an observational study found lower systolic and diastolic blood pressure after one year of oral or transdermal estrogen and cyproterone treatment.[21] Another retrospective study found that CSHT resulted in a 6 mmHg reduction in systolic blood pressure.[22] The authors concluded that this finding was more likely due to the reduction in testosterone as opposed to the increased serum levels of estradiol, as serum testosterone levels positively correlated with systolic blood pressure. Another study has speculated that lower blood pressure may also be due to the reduction of an individual’s psychological stress as they progress with their gender affirming transition.[23]

The use of antiandrogen therapy has been found to negatively alter insulin sensitivity and glucose levels in men undergoing prostate cancer treatment.[24] In one study of cisgender men

using antiandrogens for prostate cancer, a 44% increase in diabetes mellitus was found over a 10-year period.[25] While not extensively studied in the transgender population, one study compared trans women with and without orchiectomy finding that orchiectomy and CSHT was associated with less insulin resistance than CSHT alone.[26] Taken together, this suggests the use of antiandrogens has a more profound impact on insulin and blood sugars.

Impact of Estrogen on Cardiovascular Disease

To date, there has been one randomized clinical trial in cisgender men to determine if estrogen hormone therapy could be used for CVD prevention. The Coronary Drug Project randomized 1,119 men, age 30 to 64 years, with documented previous myocardial infarction (MI) to 5mg of conjugated estrogen versus 2,788 placebo.[27] Of note, this dose is similar to doses currently used for CSHT (see Table 1), making these findings applicable to transgender women. The study was stopped early after 18 months as cisgender men randomized to estrogen hormone therapy had a 2-fold increase in nonfatal MI compared to placebo.[27] Pulmonary embolism and CVD deaths were also increased in those that received estrogen. This study concluded that estrogen hormone therapy should not be used for secondary prevention in cisgender men as it increases overall CVD risk.

The Women's Health Initiative is one of the largest clinical trials in cisgender postmenopausal women to determine if hormone therapy could be used for primary prevention of CVD as well as other chronic diseases. This study used synthetic estrogen (conjugated estrogen 0.625mg) and progestin (medroxyprogesterone 2.5mg) in women with an intact uterus compared to placebo and had a parallel trial using estrogen alone in women with a hysterectomy versus placebo [28,29] Overall, there was an increased risk for coronary heart disease (HR 1.18, 95% CI, 0.95 to 1.45) and stroke (HR 1.37, 95% CI 1.07 to 1.76) in the combined hormone trial and increased risk of stroke in the estrogen alone trial (HR 1.35, 95% 1.07 to 1.70).[30] Since these trial results, there have been additional analyses suggesting that the timing of initiating hormone therapy is a key determinant of a women's CVD risk, with the study finding a lower RR in women closer to the age of menopause.[30] While not directly applicable to transgender women, the timing hypothesis may help with the understanding that estrogen when given to a younger women may not imply more CVD risk.

With respect to transgender women receiving estrogen therapy, there has been no randomized clinical trial, therefore data is limited to observation and cohort studies. In 2018, a nationwide US survey was distributed across 22 states and included questions about transgender. Of those that were surveyed, 0.57% identified as transgender.[2] The analysis was stratified by transgender women and men with the opportunity to compare to cisgender women and men. The study found that transgender women had higher odds of reporting an MI than cisgender women (OR 2.9; 95% CI, 1.6 to 5.3; $P < 0.001$); however, this was not seen when transgender women were compared to cisgender men.[2]

A more established association between CSHT and MI was found after a nationwide health survey of over 1.8 million adults by the Centers for Disease Control and Prevention.[31] All transgender individuals receiving CSHT had significantly higher rates of MI compared to their cisgender counterparts. After adjusting for CVD risk factors, transgender women had more than a two-fold increase in MI compared to cisgender women. Transgender women

when compared to cisgender men had no significant difference in MI. Taken together, this suggests that the delay in CVD onset that young cisgender women have compared to cisgender men is lost by CSHT. Furthermore, while there were few reported CVD-related deaths, 96% (23 of 24) occurred in transgender women.[31] Most recently, a Dutch analysis of 2,517 transgender women using estrogen CSHT followed for an average of 9 years found transgender women had twice as many strokes as cisgender women (29 vs 12) and MIs (30 vs 13).[32]

Synthetic ethinyl estradiol and conjugated equine estrogens were widely used CSHT in Europe prior to 2003; however, given safety concerns about its prothrombotic potential most providers have now switched to oral and transdermal estradiol and parenteral estradiol valerate. A retrospective study of 303 transgender women on combined treatment with oral ethinyl estradiol (100 mcg/day) and cyproterone acetate (100 mg/day) found the incidence of having a thromboembolic event was 45 times more likely compared to a similar reference group of the population not on estrogen.[33] In another retrospective study of transgender women in the United Kingdom, transgender women using oral conjugated equine estrogen experienced significantly more thromboembolic events compared to those using estrogen valerate or ethinyl estradiol (4.4 vs 0.6 vs 0.7%, p=0.026).[34]

Transgender Men: Masculinizing Hormone Therapy

In those born anatomically male, testosterone is the primary sex hormone. Testosterone is part of a class of hormones called androgens, which is produced mainly in the testes and in part in the adrenal glands. Testosterone plays a central role in sexual and reproductive development of a man, such as development of male sexual organs in utero, secondary sex characteristics such as deepening of the voice, body hair growth, body hair, and broadening of the shoulders, sex drive, sperm production. In addition, testosterone plays a role in regulating muscle mass, fat distribution, erythrocyte production, and bone mass.[35,36] Studies have also shown testosterone is involved with overall health and well-being in cisgender men.[37] Testosterone therapy for transgender men causes male-pattern hair growth, deepening of the voice, increased in overall body mass, muscle mass, and fat mass.[38] CSHT often also causes clitoral enlargement, decrease in breast tissue, development of acne, and, for some, increase in sexual desire.[39–41] Transgender men undergoing hormone therapy report less anxiety, dissociation, stress, and overall better gender dysphoria-related mental health. [42]

Hormone masculinization therapy with testosterone in transgender men can be administered through a variety of methods. Parenteral and transdermal administration of testosterone have proven to be both equally effective to achieve masculinization and serum testosterone values in the range of 300–1000 ng/dl in transgender men.[38,43] Guideline for testosterone therapy follow similar treatment principles as those used to treat hypogonadism in cisgender men.[44] The goal of masculinization hormone therapy is to achieve serum testosterone levels to achieve secondary sex characteristics. Current dosing recommendations include administration of intramuscular or subcutaneous testosterone enanthate or cypionate 50-100mg weekly or 100-200mg every 10-14 days.[45] Serum testosterone levels are measured between administration, although clinicians may elect to measure serum

testosterone 24 hours after injection and prior to the next dose. Transdermal testosterone in the form of a gel (1%) or patch may be used at 2.5-10g/day and 2.5-7.5mg/day, respectively. Higher doses may achieve the desired masculinization earlier in treatment, but side effects must be considered.

Impact of Testosterone on Cardiovascular Risk Factors

With testosterone CSHT, transgender men may develop risk factors such as hypertension, hyperlipidemia, and obesity that may lead to a higher likelihood of developing cardiovascular disease. Long term use of testosterone was found to increase visceral mass and decrease subcutaneous fat mass over time [46] Several studies report increase in systolic and diastolic blood pressure, triglycerides, LDL-C, and decreased HDL-C.[47,48] A study examining the administration of long-acting testosterone found significant decrease in luteinizing hormone, prolactin, sex hormone binding globulin, increased body mass index, hemoglobin, and hematocrit levels.[49] After one year of CSHT, transgender men were observed to have increased homocysteine and leucocyte levels, with a higher increase in mean maximum carotid intimal media thickness.[50] In a 2016 systematic review and meta-analysis of 29 studies, transgender men on oral testosterone-based treatment had significantly increased triglyceride levels (mean 21.4 mg/dL, 95% CI 0.14 to 42.6) at 3 to 6 months and at ≥24 months.[19] Transgender men were also found to have decreased adiponectin levels, which is associated with insulin resistance and higher cardiovascular risk. [51] C-reactive protein levels, an inflammatory marker associated with CVD risk, were also found to be increased in transgender men.[52]

Impact of Testosterone on Cardiovascular Disease

Evidence to date is mixed with respect to testosterone therapy and CVD risk in transgender men. Additionally, there has not been strong evidence of the effect of testosterone on stroke in transgender men. Recent studies in cisgender men receiving testosterone therapy have found increased coronary plaque burden and CVD mortality.[53,54] However, these studies include cisgender men with testosterone deficiency, which in itself has been associated with adverse metabolic profiles and an increased CVD risk.[55] A large cross-sectional study found that transgender men had a greater than 4-fold increase in MI compared to cisgender women and a 2-fold increase risk of MI compared to cisgender men.[31] In a recent Dutch cohort, transgender men receiving CSHT had a three-fold increase for MI compared to cisgender women (11 vs 3).[56]

On the other hand, the long term health effects of transgender men using testosterone therapy for an average of 10-years found no increased rates of CVD, including MI, stroke or deep venous thrombosis.[57] While this study was a single-center cross-sectional study of 50 transgender men, it concluded that testosterone therapy for CSHT is safe. Similarly, in a case-control study of 138 transgender men, age- and gender matched, the rates of MI and CVD were similar.[58] Notably, most studies including those previously mentioned are among younger transgender men (average age 40) when there is lower CVD risk. Further studies on older transgender men (>65 years) and CSHT are needed.

Conclusion

Although transgender individuals represent a rapidly growing population in the United States and Europe, the association between CSHT and the incidence of CVD events remains largely understudied with most research based on cross-sectional and case-control studies. Additionally, the long-term health effects of CSHT are largely unknown with current research studies evaluating up to 10-years of use. While more research and clinical trials are needed, the current available evidence suggests that the impact of CSHT on the cardiovascular system is more profound in transgender woman with higher risk for adverse cardiovascular profiles and CVD events. There is a need for additional research to better understand the association between CSHT and CVD. Future studies should include randomized controlled trials comparing various routes and formulations of CSHT and CVD in both transgender men and transgender women.

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Highlights

- Cardiovascular disease is the leading disease-specific cause of death for transgender people.
- The cross-sex hormone therapy that is necessary to achieve physical change comes with specific implications and risks related to cardiovascular disease.
- The impact of cross-sex hormone therapy on the cardiovascular system is more profound in transgender women, who have a higher risk of adverse cardiovascular profiles and cardiovascular events.
- Research on the long-term health effects of cross- sex hormone therapy (beyond 10 years of use) is needed.

Table 1:

Overview of Cross-Sex Hormone Therapy

	Hormone Treatment	Dose	Target Serum Level
Feminizing HT			
Estrogen	Estradiol, oral Estradiol, transdermal Estradiol Cypionate, IM Estradiol Valerate, IM	2-6mg/day 100-400mcg, 2mg every 2 weeks, 20 mg every 2 weeks	100-300 mg/dL
Antiandrogen	Spironolactone Cyproterone Acetate	50-400 mg/day 50-100 mg/day	Testosterone <55ng/dl
Progesterone	Medroxyprogesterone acetate Micronized progesterone	2.5-8 mg/day 100-200 mg/day	N/A
Masculinizing HT			
Testosterone	Testosterone Undecanoate, Oral * Testosterone Enanthate or Cypionate, SC or IM Testosterone Undecanoate, SC or IM Implant (SC) Transdermal Gel (1%) Transdermal Patch	160–240 mg/day 50–100 mg/week or 100–200 mg/10–14 days 1000mg/12 weeks 75 mg/pellet 2.5-10g/day 2.5-7.5me/day	300–1000 ng/dl

* Not available in the united states, IM = intramuscular; SC = subcutaneous