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Cardiovascular health in transgender people

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Abstract
This review examines the relationship between exogenous sex steroids and cardiovascular events and surrogate markers in trans (transgender) people. Data from trans populations is compared to data from postmenopausal women and hypogonadal men when appropriate. In an age-adjusted comparison with cisgender people, trans people appear to have an increased risk for myocardial infarction and death due to cardiovascular disease. It is uncertain whether hormone therapy in trans people affects their risk of stroke. In studies that followed trans people on hormone therapy, the rates of myocardial infarction and stroke were consistently higher in trans women than trans men. There is strong evidence that estrogen therapy for trans women increases their risk for venous thromboembolism over 5 fold. Extrapolating from studies of hormone therapy in postmenopausal women, transdermal estrogen likely carries a lower risk for venous thromboembolism than oral estrogen. Regarding red blood cells, testosterone therapy increases hemoglobin in trans men, and lowering testosterone in trans women has the opposite effect. Regarding blood pressure, the effects of hormone therapy on systolic blood pressure in trans women are inconsistent, with most studies showing an increase. In trans men, testosterone therapy consistently increases systolic blood pressure and may increase diastolic blood pressure. For lipids, hormone therapy may increase triglycerides in both trans women and men. In trans men, testosterone therapy also may increase LDL-cholesterol and decrease HDL-cholesterol.

Keywords Blood pressure · Cardiovascular · Myocardial infarction · Stroke · Transgender · Venous thromboembolism

1 Introduction

The relationship between sex steroids and cardiovascular health remains a topic of great interest regardless of sex or gender identity. Although thousands of studies have been conducted in this arena, many gaps remain in our knowledge. When it comes to studying cardiovascular outcomes in trans individuals on hormone therapy, several limitations present significant challenges. For example, take the age of the study population. Whereas individuals over age 50 carry the highest burden of cardiovascular events such as myocardial infarctions and strokes, most transgender people begin hormone therapy at much earlier ages when their overall risk for cardiovascular events is quite low. Second, given low numbers of incident cardiovascular events, large population studies would be needed to statistically capture associations between hormone use and cardiovascular outcomes.

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This review focuses on cardiovascular events and surrogate markers in trans people on hormone therapy who may or may not have undergone gender affirmation surgeries. The cardiovascular events include myocardial infarction, stroke, and venous thromboembolism/pulmonary embolus. The surrogate markers include blood pressure, lipid concentrations and hemoglobin/hematocrit levels. The cardiovascular event and surrogate marker data are summarized by gender in Tables 1 and 2. To provide context and biological plausibility, the results from studies of trans populations will be compared to those from studies of hormone therapy in postmenopausal women and hypogonadal men, when applicable. Nevertheless, the comparisons between these populations should be viewed with caution as hormone regimens vary markedly among the populations, particularly for trans women who are typically prescribed doses of estrogen much higher than those used in postmenopausal women.

Teasing apart the cardiovascular effects of hormone therapy in trans patients is complicated as various treatment regimens have different effects. For trans women who have not undergone an orchiectomy, standard treatment consists of estrogen plus an antiandrogen. The antiandrogen most commonly used in European studies has been cyproterone

Table 1 Effects of hormone therapy on cardiovascular events

Event	Risk		Comments
	Trans women	Trans men	
Myocardial infarction	Probable increase	Unknown	• Rates are much lower in trans men than in trans women • In trans women ethinyl estradiol may confer a greater risk
Stroke	Probable increase	No increase	• Rates are much lower in trans men than in trans women • In trans women avoid ethinyl estradiol • In post-menopausal women, the risk is dose dependent and oral estrogen formulations confer a greater risk than transdermal
Venous thromboembolism	Definite increase	No increase	• Rates are 0–5% in trans women and 0–0.34% in trans men • In post-menopausal women, oral estrogen formulations confer a greater risk than transdermal

acetate (CPA) whereas in the United States it has been spironolactone. CPA has progestogenic properties and competes with testosterone and dihydrotestosterone for the androgen receptor [1]. Spironolactone acts as an aldosterone and androgen antagonist and also inhibits 5α reductase activity [2]. In terms of systemic estrogen therapy, historically the three most common types were 17β-estradiol (which is the native human hormone), ethinyl estradiol (EE - a synthetic derivative of estradiol) and conjugated equine estrogens (CEE) which contain a mixture of several estrogens. Ethinyl estradiol and CEE are usually taken orally whereas 17β-estradiol can be taken orally, transdermally, sublingually, or intramuscularly, although oral and transdermal routes predominate. Oral formulations undergo first pass metabolism by the liver whereas the others do not. For both trans women and men, intramuscular administration of estradiol or testosterone esters, respectively, is associated with supraphysiological levels of the hormone a few days after the injection [3]. To further complicate the study of hormone therapy, progestogens are commonly used in pre and post-menopausal women and are occasionally used in trans populations. In trans women, progestogens are occasionally used to suppress androgens and some trans women take them based upon anecdotal evidence that they further stimulate breast growth, although scientific data is lacking. Progestogens are occasionally used in trans men who continue to have menses on testosterone monotherapy or for those who are unable to obtain a GnRH-analog. Certain progestogens interact with not only progesterone receptors but also with the androgen, estrogen and glucocorticoid receptors [4].

Much of the data regarding post-menopausal women comes from the Women's Health Initiative (WHI), a study with over 27,000 subjects recruited between ages 50–79 [5]. Hormone treatment in the WHI consisted of an oral CEE (0.625 mg/day) with or without continuous oral medroxyprogesterone (MPA) (2.5 mg/day) depending on the presence of an intact uterus. The findings of the WHI are

Table 2 Effects of hormone therapy on cardiovascular surrogate markers

Measure	Effect		Comments
	Trans women	Trans men	
Systolic blood pressure	Inconsistent	Increase	• In trans women, most studies show a mean increase of 6–18 mmHg • In trans men, the mean increase ranges from 1 to 13 mmHg
Diastolic blood pressure	No change or increase	Increase	• In trans women, most studies show an increase of 3–6 mmHg • In trans men, the mean increase ranges from 1.5–4 mmHg
Hemoglobin/hematocrit	Decrease	Increase	• Effects are due to testosterone rather than estrogen • In trans men, erythrocytosis is uncommon • In trans men, the increase may be greater with the intramuscular esters or undecanoate versus transdermal
Lipids			
Total cholesterol	Inconsistent	Inconsistent	• In trans men, most studies show an increase
LDL cholesterol	Inconsistent	Increase	
HDL cholesterol	Inconsistent	Decrease	
Triglycerides	No change or increase	Increase	

complex as the results often varied by age when subjects began hormone therapy.

The relationship between endogenous sex hormones and cardiovascular health is complicated. In cisgender women, estrogen and other ovarian hormones appear to have a protective effect [6, 7]. A meta-analysis found that women who underwent an early bilateral oophorectomy had more than a 2 fold higher risk of cardiovascular disease [6]. Likewise, a meta-analysis and systematic review found that the age of onset of menopause is inversely associated with cardiovascular outcomes [7]. As compared to women who began menopause after age 45, women who began menopause before age 45 had an increased cardiovascular disease mortality [RR 1.19 (95% CI, 1.08–1.31)] and coronary heart disease mortality [RR 1.11 (95% CI, 1.03–1.20)] with no difference in stroke mortality [RR 0.99 (95% CI, 0.92–1.07)]. A limitation to this systematic review was that hormone use was not specified or adjusted for in many of the included studies.

2 Cardiovascular disease

Data on whether hormone therapy affects the incidence of cardiovascular disease in trans people is limited due to the young age when many patients begin hormone therapy, the lack of long term follow-up, the lack of robust control groups and the small number of events such as myocardial infarction. For these reasons, data from cisgender women may be informative.

2.1 Postmenopausal women

During the intervention phase of the WHI study, hazard ratios for all cardiovascular events were increased at 1.13 (95% CI, 1.02–1.25) for the CEE + MPA trial and 1.11 (95% CI, 1.01–1.22) for the CEE alone trial [5]. The hazards ratios for total myocardial infarction, coronary artery bypass grafting/percutaneous coronary intervention and cardiovascular deaths were not increased [5]. For the CEE alone trial, the hazards ratios for myocardial infarction increased by decade of age (0.55 for 50–59 years, 0.95 for 60–69 years and 1.24 for 70–79 years) [5]. A Cochrane review found that hormone therapy was associated with a reduced risk of coronary heart disease [RR 0.52 (95% CI, 0.29–0.96)] in post-menopausal women who commenced hormone therapy less than 10 years after menopause [8]. Hormone therapy had no effect on coronary heart disease in postmenopausal women who began hormone therapy more than 10 years after menopause [RR 1.07 (0.96–1.20)] or on death due to cardiovascular causes in post-menopausal women with pre-existing cardiovascular disease [RR 1.00 (0.78–1.29)] [8].

2.2 Cisgender men

Trials of testosterone therapy in men with low or borderline low serum testosterone levels have shown inconsistent findings. Six out of seven systematic reviews and meta-analyses found that testosterone therapy did not increase the incidence of cardiovascular events with summary estimates ranging from 1.07–1.82 [9]. Two individual studies did report adverse cardiovascular events associated with testosterone treatment [10, 11]. In a randomized controlled trial (RCT) of topical testosterone treatment in 209 elderly men with limitations in mobility, the trial was stopped prematurely as there was a 5.8 fold (95%CI 2.0–16.8) increased adjusted odds ratio of cardiovascular-related events which included peripheral edema, elevated blood pressure, arrhythmias and electrocardiographic changes [10]. This study was not powered to detect differences in atherosclerosis-related events such as myocardial infarction, sudden death, angioplasty, coronary artery bypass grafting and stroke. The second study examined the incidence rate of myocardial infarction in men who received a testosterone prescription within a large health-care database [11]. In men ≥65 years old and those <65 years with pre-existing heart disease, the rate ratios of myocardial infarction were 2.2 and 2.9, respectively, during the 90 days following the receipt of a testosterone prescription [11]. In a RCT of 308 older men with low or low-normal total testosterone levels (100–400 ng/dL) and free testosterones <50 pg/mL, topical testosterone administration for 3 years did not alter the rates of change of coronary artery calcium or common carotid artery intima media thickness [12].

2.3 Trans people

In a robust study that compared the health status of trans (n = 691) and cisgender (n = 150,765) adults in the United States using a probability sample from data from the Behavioral Risk Factor Surveillance System, the adjusted odds ratio for myocardial infarction was increased at 1.82 (95% CI, 1.22–2.72) [13]. The adjusted odds ratio for angina/coronary heart disease was not statistically increased at 1.37 (95% CI, 0.83–2.25) [13]. Although the article did not break down the trans population by gender, data obtained from the authors showed very similar rates by gender. In another study that retrospectively combined 324 trans men and women who all underwent gender-affirmation surgery, the adjusted hazard ratio for death by cardiovascular disease was more than double [2.5 (95% CI, 1.2–5.3)] that of age and birth-sex matched controls from the general population [14].

2.4 Trans women

For trans women, a meta-analysis of 1073 individuals on estrogen therapy (and an antiandrogen if testes were present)

found 14 cases of myocardial infarction in three studies with variable durations of follow-up [15]. In a retrospective study of 816 trans women in an older era in which oral ethinyl estradiol + CPA was the common treatment regimen, there were 10 cases of myocardial infarction in which 6 were fatal [16]. As compared to the general male population, the standardized incidence ratio for myocardial infarction was 0.50 (95% CI, 0.24–0.91) [16]. In a study of 966 trans women treated with either ethinyl estradiol or transdermal estradiol + CPA for a mean of 19.4 years, there was an increased standardized mortality ratio of 1.64 (95% CI, 1.43–1.87) for ischemic heart disease [17].

In a retrospective study of 214 trans women on different formulations of oral and transdermal estrogen for a mean of 7.7 years, there were 3 cases of myocardial infarction with an average age of 48 at the time of the event [18]. The rates of myocardial infarction were 4.7/1000 persons prior to hormone therapy and 18.7/1000 persons during hormone therapy [18]. As compared to age-matched cisgender men, the rates were statistically no different [18]. In a retrospective study of 50 trans women status post gender affirmation surgery who were on different formulations of oral and transdermal estrogen for an average of 9.2 years, there was one case of myocardial infarction in a 43 year old smoker [19].

2.5 Trans men

For trans men, a meta-analysis of 478 individuals on testosterone therapy found 1 case of myocardial infarction in three studies with variable durations of follow-up [15]. In a retrospective study of 293 trans men treated with testosterone esters IM or oral testosterone undecanoate for 2418 patient years, there was one case of myocardial infarction [16]. In a retrospective study of 365 trans men treated with various formulations of testosterone for a mean of 18.9 years, there was no difference in mortality due to ischemic heart disease as compared to a birth-sex matched population [17]. In a retrospective study of 50 trans men status post gender affirmation surgery who were on testosterone therapy for a total of 496 treatment years, there were no cases of myocardial infarction [19]. Similarly, in a retrospective study of 138 trans men primarily on testosterone esters or IM testosterone undecanoate for a mean of 9.4 years, there were no cases of myocardial infarction [18].

3 Stroke

Data on whether hormone therapy affects the incidence of stroke in trans people is limited due to the same reasons listed above for cardiovascular events. Therefore, data from cisgender women may be informative.

3.1 Postmenopausal women

There is strong evidence that hormone therapy in older postmenopausal women is associated with an increased risk of stroke. During the intervention phase of the WHI study, hazard ratios for stroke were 1.37 (95% CI, 1.07–1.76) for the CEE + MPA trial and 1.35 (95% CI, 1.07–1.70) for the CEE alone trial [5]. This translates to an additional 9–11 strokes/10,000 person-years [5]. A Cochrane review found that hormone therapy was associated with an increased risk of stroke [RR 1.21 (95% CI, 1.06–1.38)] in post-menopausal women who began hormone therapy more than 10 years after menopause [8]. Hormone therapy had no effect on stroke in postmenopausal women who commenced hormone therapy less than 10 years after menopause [RR 1.37 (95% CI, 0.80–2.34)] or in post-menopausal women with pre-existing cardiovascular disease [RR 1.09 (95% CI, 0.89–1.33)] [8].

The risk of stroke with hormone therapy in postmenopausal women appears to be related to both dose and route of delivery. In a nested case-control study of women aged 50–79 from the United Kingdom's General Practice Research Database, adjusted rate ratios for stroke were increased for oral (conjugated equine or estradiol) but not transdermal formulations of both estrogen only or combination hormone therapy [20]. Further analysis found that the adjusted rate ratio for stroke was increased for women on higher doses (>50 μg) of transdermal estrogen. The adjusted rate ratios were 0.81 (95% CI, 0.62–1.05) for low dose transdermal, 1.89 (95% CI, 1.15–3.11) for high dose transdermal, 1.25 (95% CI, 1.12–1.40) for low dose oral and 1.48 (95% CI, 1.16–1.90) for high dose oral [20]. High dose estrogen was defined as >0.625 mg of CEE or > 2 mg estradiol.

In a case-control study of post-menopausal women 51–62 years old, rates of ischemic stroke were related to estrogen dose, route of estrogen administration and type of progestogen [21]. Adjusted odds ratios for ischemic stroke for current hormone therapy users compared to non-users were 1.58 (95% CI, 1.01–2.49) for oral estrogen and 0.83 (95% CI, 0.56–1.24) for transdermal estrogen. Non-pregnane derivatives (nomegestrol acetate and promegestone) were associated with an increased odds ratio of ischemic stroke of 2.25 (95% CI, 1.05–4.81) whereas no differences were noted with progesterone, pregnane derivatives (medroxyprogesterone acetate, dydrogesterone, medrogestone, chlormadinone acetate and cyproterone acetate) or nortestosterones [21]. In addition, higher doses of oral estrogen correlated to a greater risk of ischemic stroke. As compared to non-users, odds ratios were 1.39 (95% CI, 1.00–1.99) for low dose estrogen users, 1.84 (95% CI, 1.02–3.30) for intermediate dose users and 2.41 (95% CI, 1.43–4.07) for high dose users. High dose estrogen was defined as ≥2 mg/day of oral estrogen or > 50 μg/day of transdermal estrogens.

3.2 Trans women

A study based on data from the Behavioral Risk Factor Surveillance System found that the adjusted odds ratio for stroke was not statistically different for trans versus cisgender people [1.75 (95% CI 0.93–3.29] [13]. Although the article did not break down the transgender population by gender, data obtained from the authors showed very similar rates by gender. For trans women, a meta-analysis of 859 individuals on estrogen therapy found 8 cases of stroke in two studies with variable durations of follow-up [15]. In a retrospective study of 816 trans women in an older era in which oral ethinyl estradiol + CPA was the common treatment regimen, there were 5 cases of transient ischemic attack and 1 case of intracranial hemorrhage [16]. As compared to the general male population, the standardized incidence ratio for cerebrovascular disease for trans women was 1.71 (95% CI, 0.63–3.88) [16]. In a study of 966 trans women treated with either ethinyl estradiol or transdermal estradiol + CPA for a mean of 19.4 years, there were 5 deaths from stroke which occurred before age 60 in two subjects and at age 60, 62 and 75 in the remainder [17]. As compared to a control group stratified by age and birth-sex, the standardized mortality rates for fatal stroke were 1.26 (95% CI, 0.93–1.64) for all five subjects but 2.11 (95% CI, 1.32–3.21) for those aged 40–64 years [17]. All cases of fatal stroke were in users of ethinyl estradiol. In a retrospective study of 214 trans women on different formulations of oral and transdermal estrogen for a mean of 7.7 years, there were 5 cases of TIA/cerebrovascular disease with an average age of 51 at the time of the event [18]. The rates of TIA/cerebrovascular disease were 4.7/1000 persons prior to hormone therapy and 23.4/1000 persons during hormone therapy [18]. As compared to age-matched population controls, the rates were statistically higher when compared to cisgender men but not cisgender women [18]. In a retrospective study of 50 trans women status post gender affirmation surgery who were on different formulations of oral and transdermal estrogen for an average of 9.2 years, there were two cases of cerebral thrombosis (in smokers aged 46 and 58) and one transient ischemic attack in a 33 year old at the time of gender affirmation surgery [19].

3.3 Trans men

For trans men, a meta-analysis of 340 individuals on testosterone therapy found no cases of stroke in two studies with variable durations of follow-up [15]. In a retrospective study of 293 trans men treated with testosterone esters IM or oral testosterone undecanoate for 2418 patient years, there were no cases of cerebrovascular events [16]. In a retrospective study of 365 trans men treated with various formulations of testosterone for a mean of 18.9 years, there were no deaths from stroke [17]. In a retrospective study of 50 trans men status post gender affirmation surgery who were on testosterone therapy for a total of 496 treatment years, there were no cases of cerebrovascular disease [19]. Similarly, in a retrospective study of 138 trans men primarily on testosterone esters or IM testosterone undecanoate for a mean of 9.4 years, there were no cases of TIA/cerebrovascular disease [18].

4 Venous thromboembolism

There is convincing evidence that estrogen therapy increases the risk for venous thromboembolism (VTE) in both cisgender and transgender women. Many centers providing trans care do not prescribe or recommend EE or CEE due to concerns about thrombosis risk. Nevertheless, much of the existing data on estrogens and thrombosis risk in trans-women derive from older studies in which CEE and EE were widely used, so concerns raised by these data should be treated with a degree of caution.

4.1 Postmenopausal women

Large studies in postmenopausal women have found differences in rates of VTE depending on the route of administration of estrogen, whether a progestogen was part of the regimen and type of progestogen. During the intervention phase of the WHI study, hazard ratios for deep vein thrombosis were 1.87 (95% CI, 1.37–2.54) for the CEE + MPA trial and 1.48 (95% CI, 1.06–2.07) for the CEE alone trial [5]. This translates to an additional 7–12 deep vein thromboses/10,000 person-years [5]. The hazard ratio for pulmonary embolism was only increased for the CEE + MPA trial at 1.98 (95% CI, 1.36–2.87). A Cochrane review found that hormone therapy was associated with an increased risk of venous thromboembolism in all populations of post-menopausal women: those who commenced hormone therapy less than 10 years after menopause [RR 1.74 (95% CI, 1.11–2.73)] or more than 10 years after menopause [RR 1.96 (95% CI, 1.37–2.80)] or those with pre-existing cardiovascular disease [RR 2.02 (95% CI, 1.13–3.62)] [8]. This increased risk would represent 5–12 additional cases of venous thromboembolism per 1000 people [8]. The increased risk was largely driven by women on combination hormone therapy.

In a case-control study of post-menopausal women 45–70 years old, rates of venous thromboembolism were related to route of estrogen administration and type of progestogen [22]. Adjusted odds ratios for VTE for current hormone therapy users compared to non-users were 4.2 (95% CI, 1.5–11.6) for oral estradiol and 0.9 (95% CI, 0.4–2.1) for transdermal estrogen. Non-pregnane derivatives (nomegestrol acetate and promegestone) were associated with an increased odds ratio of VTE of 3.9 (95% CI, 1.5–10.0) whereas no differences were noted with micronized progesterone or pregnane derivatives

(medroxyprogesterone acetate, dydrogesterone, medrogestone, chlormadinone acetate and cyproterone acetate).

4.2 Trans women

For trans women, a meta-analysis of 1767 individuals on estrogen therapy found VTE rates of 0–5% in ten studies with variable durations of follow-up [15]. In a retrospective study of 816 trans women in an older era in which ethinyl estradiol + CPA was the common treatment regimen, there were 45 cases of VTE and/or PE including 36 without an additional risk factor such as surgery or trauma [16]. As compared to the general male population, the standardized incidence ratio for VTE for trans women was 19.56 (95% CI, 12.27–26.18). In a retrospective study of 214 trans women on different formulations of oral and transdermal estrogen for a mean of 7.7 years, rates of VT and/or PE were 9.2/1000 persons prior to hormone therapy and 60.7/1000 persons during hormone therapy [18]. In the eleven cases of VTE, additional risk factors were present in all but one case: smoking ($n = 7$), immobilization for surgery ($n = 3$) and/or a clotting disorder ($n = 1$) [18]. In a retrospective study of 50 trans women status post gender affirmation surgery who were on different formulations of oral and transdermal estrogen for an average of 9.2 years, there was 1 case of DVT in a 52 year old former smoker on oral conjugated estrogens [19]. In a retrospective chart review of 676 trans women who were treated with a hormone regimen including oral estradiol for a mean of 1.9 years, there was only one case of VT or PE [23]. The case was a PE in a non-smoking trans woman in her 20s on estradiol 4 mg/day and spironolactone 200 mg/day with no additional risk factors other than a BMI of 37 [23]. In a retrospective study of 162 trans women, including twelve with activated protein C (APC) resistance, treated with transdermal estradiol + CPA for a mean of 53 months, there were no cases of VTE [24]. In a retrospective study of 332 trans women on three different oral formulations of estrogen, the rate of VTE was seven fold higher in women on CEE as compared to those on estrogen valerate or EE [25].

4.3 Trans men

For trans men, a meta-analysis of 771 individuals on testosterone therapy found VTE rates of 0–0.34% in eight studies with variable durations of follow-up [15]. In a retrospective study of 293 trans men treated with testosterone esters IM or oral testosterone undecanoate for 2418 patient years, there was one case of venous thrombosis which occurred postoperatively [16]. In a retrospective study of 50 trans men status post gender affirmation surgery who were on testosterone therapy for a total of 496 treatment years, there were no cases of DVT [19]. In a retrospective study of 89 trans men, including five with APC resistance, treated with testosterone undecanoate IM for a mean of 47 months, there were no cases of VTE [24].

4.4 Thrombotic factors

The mechanisms whereby estrogen therapy increases the risk of VTE is thought to be related to a more thrombotic state, a decrease in blood flow and/or changes to the vessel walls. Two studies in trans populations have examined the thrombotic factors [26, 27]. One small study measured changes in hemostatic variables in both trans women and trans men treated with hormone therapy [26]. For trans women treated for 4 months, oral ethinyl estradiol (EE) + CPA markedly increased APC resistance (1.2 to 4.1) while transdermal (Td) estradiol + CPA and CPA alone modestly increased APC (1.3 to 2.0 and 1.4 to 1.8, respectively) [26]. Trans women ($n = 14$) on the EE + CPA treatment had increased levels of protein C antigen (107 to 117%) and decreased levels of protein S total antigen (115 to 82%) with no significant changes observed in trans women on the CPA alone ($n = 8$) or Td estradiol + CPA ($n = 14$) [26]. The authors commented that the APC resistance values in trans women on EE + CPA treatment were comparable to individuals who are heterozygous and homozygous for factor V Leiden. For trans men ($n = 14$), treatment with testosterone esters IM had a mild antithrombotic effect with a decrease in APC resistance (2.0 to 1.3) and increase in protein S total antigen (105 to 118%) [26]. Another study found that trans women on 4 months of treatment with EE + CPA ($n = 15$), but not Td estradiol + CPA ($n = 15$), had decreased levels of tissue-type plasminogen activator (7.9 to 3.8 ng/mL) and plasminogen activator inhibitor-1 (25.7 to 8.9 ng/mL) [27].

5 Red blood cells

Sex steroids are strongly linked to the production of red blood cells. The approximate 10 fold difference in serum testosterone concentrations between cisgender men and women are a major determinant of the different reference ranges for hemoglobin and hematocrit between the sexes. Historically, before newer treatments became available, testosterone therapy was commonly used to treat men with certain anemias. Not surprisingly, testosterone therapy increases hemoglobin in trans men, and lowering testosterone in trans women has the opposite effect. It is unclear whether altering the hemoglobin and hematocrit in trans people has any impact on cardiovascular outcomes such as myocardial infarction, stroke, and venous thromboembolism. From a clinical standpoint, trans men on testosterone are monitored for erythrocytosis.

5.1 Trans women

In trans women, treatment with estrogen plus an antiandrogen lowers the hemoglobin and hematocrit. In the prospective European Network for the Investigation of Gender Incongruence (ENIGI) study of 53 trans women treated for 12 months, the mean hematocrit dropped from 45.2 to 42.0% in younger subjects on oral estradiol 4 mg/day + CPA and from 45.5 to 42.0% in older subjects on transdermal estradiol + CPA [28]. In a retrospective study of 150 trans women treated for 2 years with oral or transdermal estradiol + CPA, the hemoglobin dropped from 14.6 to 13.8 g/dL [29].

5.2 Trans men

Trans men on IM testosterone esters for a mean of 45 months had a higher mean hematocrit (44.9%) as compared to a population of untreated trans men with a mean hematocrit of 38.8% [30]. In trans men, the different formulations of testosterone may increase the hemoglobin and hematocrit to varying degrees, although the data is limited. In a study that compared different formulations of testosterone treatment over 1 year in 45 trans men equally divided into three groups, the rise in hemoglobin & hematocrit was less with the transdermal gel versus the IM esters or IM undecanoate [31]. In the prospective ENIGI study of 53 trans men treated with IM T undecanoate for 12 months, the mean hematocrit increased from 40.8 to 45.8% [28]. In a prospective study of 12 trans men treated for 12 months with IM testosterone undecanoate, the mean hemoglobin rose from 13.8 to 15.1 g/dL with a rise in hematocrit from 41.0 to 44.3% [32]. In a prospective study of 50 trans men treated for 12 months with various testosterone formulations, the mean hemoglobin rose from 13.3 to 15.0 g/dL with a rise in hematocrit from 39.9 to 44.2% [33]. In a study of 45 trans men treated for 2 years with IM testosterone undecanoate, the mean hemoglobin rose from 13.2 to 14.6 g/dL [34]. In a retrospective study of 97 trans men treated for 2 years with transdermal testosterone gel or IM testosterone undecanoate, the mean hemoglobin rose from 13.5 to 15.3 g/dL [29].

6 Blood pressure

6.1 Trans women

In trans women, effects of estrogen therapy on systolic blood pressure (SBP) are inconsistent, with most studies showing an increase [28, 29, 35, 36]. Studies showed either no change or an increase in diastolic blood pressure (DBP) [28, 29, 35, 36]. In the prospective ENIGI study of 53 trans women treated for 12 months, the mean SBP decreased from 125.1 to 118.8 mmHg in subjects on oral estradiol 4 mg/day + CPA and was unchanged in subjects on transdermal estradiol + CPA [28]. In a study of 20 trans women treated for 12 months with ethinyl estradiol + CPA, the mean SBP increased from 127 to 134 mmHg and the DBP increased from 70 to 76 mmHg [35]. In a study of 79 trans women treated for 2 years with transdermal estradiol + CPA, the mean SBP increased from 111 to 129 mmHg and the DBP increased from 76 to 79 mmHg [36]. In a retrospective study of 150 trans women treated for 2 years with oral or transdermal estradiol + CPA, the mean SBP increased from 115.5 to 121.9 mmHg and the DBP increased from 72.9 to 76.6 mmHg [29].

6.2 Trans men

In trans men, testosterone therapy consistently increases SBP and may increase DBP, although some DBP results did not reach statistical significance [28–30, 34–36]. In the prospective ENIGI study of 53 trans men treated with IM T undecanoate for 12 months, the mean SBP increased from 111.5 to 115.6 mmHg and the mean DBP was unchanged [28]. In a study of 45 trans men treated for 2 years with IM testosterone undecanoate, the mean SBP increased from 129 to 135 mmg Hg and no changes were observed with the DBP [34]. In a study of 43 trans men treated for 2 years with IM testosterone esters, the mean SBP increased from 111 to 125 mmg Hg and no changes were observed with the DBP [36]. In a retrospective study of 97 trans men treated for 2 years with transdermal testosterone gel or IM testosterone undecanoate, the systolic and diastolic blood pressures were unchanged [29]. Trans men treated with IM testosterone esters for 12 months had no changes to SBP or DBP [35]. Trans men on IM testosterone esters for a mean of 45 months had a higher mean SBP (117 mmHg) and DBP (69 mmHg) as compared to a population of untreated trans men with a mean SBP of 110 mmHg and DBP of 65 mmHg [30].

7 Lipids

7.1 Trans women

A meta-analysis of hormone therapy in trans women in six studies found an increase in triglycerides of 32 mg/dL (4–60 mg/dL) at 2 years only and no changes to total cholesterol, LDL-cholesterol and HDL-cholesterol [15]. Opposite effects on total cholesterol and HDL-cholesterol were observed in women treated with cyproterone acetate versus leuprolide, both in combination with transdermal estradiol [37].

7.2 Trans men

A meta-analysis of testosterone therapy in trans men found an increase in triglycerides and LDL-cholesterol and a decrease

in HDL-cholesterol [15]. The magnitude of the changes for triglycerides were 9 mg/dL (3–16 mg/dL) at 3–6 months and 21 mg/dL (0–43 mg/dL) at 24 months [15]. For LDL-cholesterol the mean increase was 11 mg/dL (6–17 mg/dL) at 12 months and 18 mg/dL (4–32 mg/dL) at ≥24 months and for HDL-cholesterol the mean decrease was 9 mg/dL (3–14 mg/dL) at ≥24 months [15]. Similarly, trans men on IM testosterone esters for a mean of 45 months had higher triglycerides and LDL-cholesterol and lower HDL-cholesterol as compared to a population of untreated trans men [30]. In a study that compared different formulations of testosterone treatment over 1 year in 45 trans men equally divided into three groups, the changes in HDL and LDL-C were less with the transdermal gel versus the IM esters [31].

8 Conclusions

In epidemiological studies, trans women (and possibly trans men) appear to have an increased risk for myocardial infarction and death due to cardiovascular disease, presumably due to hormone therapy. It is uncertain whether their risk of stroke is similar or increased. In clinical studies following trans people on hormone therapy, the rates of myocardial infarction and stroke were consistently higher in trans women than trans men. Trans women on estrogen (with or without a progestin) have a significantly increased risk for venous thromboembolism.

Given that hormone therapy is an integral part of the management of trans patients, more research is needed on the effects and risks of hormone therapy in older populations and on the safest forms of estrogen therapy in terms of type, dosing and route of delivery. It is likely that some forms of estrogen (i.e. transdermal estradiol) carry less risk for venous thromboembolism. Research is lacking on sublingual estrogen which many trans women prefer as it increases serum estrogen levels to a greater degree than oral estrogen [38]. Finally, to promote optimal cardiovascular health in trans patients, clinicians should not forget to encourage regular exercise, smoking cessation when necessary and maintenance of a normal body weight/composition.

Compliance with ethical standards

Conflict of interest Michael S. Irwig declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by the author.

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