Cardiovascular disease in transgendered people: A review of the literature and discussion of risk

Leighton J Seal[1,2,3] (iD)

Abstract

This review examines the impact of gender affirming hormone therapy used in the transgendered and non-binary populations on cardiovascular outcomes and surrogate markers of cardiovascular health. Current evidence suggests that hormonal therapy for transgendered women decreases or is neutral regarding myocardial infarction risk. There is an increased incidence of venous thromboembolism (VTE), but newer studies suggest that the risk is significantly lower than previously described. For transgendered men, there appears to be an adverse effect on lipid parameters but this does not translate into an increased risk of cardiovascular disease above that of general male population. In all transgendered people, risk factor interventions such as smoking cessation, weight management and treatment of co-morbid conditions are important in optimising cardiovascular health. The effect of gender affirming hormonal therapy in transgendered people is difficult to interpret due to the variety of hormone regimens used, the relative brevity of the periods of observation and the influence of confounding factors such as the historical use of less physiological, oestrogens such as conjugated equine oestrogen and ethinylestradiol which are more pro-thrombotic than the 17β oestradiol that is used in modern practice.

Introduction

Hormone replacement therapy for the majority of transpeople is an important part of their transition process. It is known that sex steroid therapy is associated with cardiovascular risk[1–6] but there is poor quality evidence of the extent of this risk in the transgendered population. Cardiovascular risk in this population has been examined by meta-analyses;[7–9] however, the literature has been extended with the recent publication of further large studies looking at cardiovascular outcomes in transgendered people, both in the USA[10–12] and Europe.[13]

This review will examine the current evidence on the impact of gender affirming hormonal therapy in the binary transgendered population, on cardiovascular health and surrogate markers of cardiovascular risk such as lipid profile and thrombotic risk. It will also put these findings in the context of the recent studies and also discuss non-hormonal factors that may contribute to adverse cardiovascular outcomes in this population.

Methods

A literature search of the current English language literature was made using the Pub Med database using key words to identify articles relating to cardiovascular health in transgendered people. Key words were transgender, transgendered, transsexual, transman,

[1]St George's Hospital Medical School, London, UK
[2]St George's University Hospitals NHS Foundation Trust, London, UK
[3]Gender Identity Clinic, Tavistock and Portman NHS Foundation Trust, London, UK

Corresponding author:
Leighton John Seal, Gender Identity Clinic, Tavistock and Portman NHS Foundation Trust, 179-183 Fulham Palace Road, London W6 8QZ, UK.
Email: lseal@sgul.ac.uk

transmen, transwoman, transwomen, non-binary, myocardial infarction, MI, thromboembolism, pulmonary embolism, deep venous thrombosis, TE, DVT, PE, stroke, cardiovascular, lipid, metabolic, and meta-analysis.

Where studies were included in a meta-analysis these data were used to give an overview of the effect of gender affirming hormone treatment on an outcome.

Cardiovascular disease and gender

Cardiovascular disease has a major impact on mortality. In the 20th century, it was the major cause of mortality and has only recently been overtaken by malignancy as the leading cause of death in the UK.[14] The risk factors for developing cardiovascular disease have long been divided into modifiable and non-modifiable factors. One of the previously non-modifiable risk factors was gender. There has been and extensive literature on the gender differences in cardiovascular risk,[15,16] which have usually been attributed to the difference in hormonal *mileu* between males and females.

Gender terminology and gender dysphoria

People who remain in the gender role they were assigned at birth are termed cisgendered women (a person who was birth assigned female who remains in a female gender role) and cisgendered men (a person who was birth assigned male who remains in a male gender role). An increasing number of people are questioning the gender they were assigned at birth which is termed gender nonconformity. Many of these people decide to change their social gender role to one that is more concordant with their internal sense of gender, the majority of individuals make a binary transition from one gender role to a role that would be viewed as the opposite gender role (from birth assigned male to female; a transgendered woman or from birth assigned female to male; a transgendered man) and a smaller number of people transition to a gender role that is not defined by male or female (non-binary). The majority of people who transition gender role use gender affirming hormonal therapy to achieve the secondary sexual characteristics of their desired gender and so their hormone *mileu* is different to their birth assigned gender.

Gender dysphoria is not a rare condition with an impression of rising incidence. Previous estimates of the incidence ranged between 1:74401 and 1:30,000 for birth assigned males and 1:31,153 to 1:10,000 for birth assigned females.[17] A meta-analysis estimated the prevalence to be 6.8/100 000 for transgendered women and 2.6/100,000 for transgendered men.[18] More up-to-date studies suggest that the incidence is higher, with 0.5–1.3% of birth-assigned males and 0.4–1.2% birth-assigned females identify as a transgendered person.[19]

A recent study suggested that approximately 10% of people attending a large single centre gender clinical have a non-binary gender identity.[20] The transgendered population is growing, cardiovascular death has been identified as a significant cause of mortality in this population,[10,12,21–24] and so its management is part of main stream medicine, and it is not limited to specialist centres.

Cardiovascular risks and endogenous sex steroids

It has been observed across many study populations that males have higher cardiovascular mortality than females certainly until menopause.[15,16] After menopause, female cardiovascular mortality increases with advancing age[25,26] and so it is argued that oestrogen is cardio-protective and testosterone is atherogenic. It is known that endogenous ovarian hormone production protects cisgendered women from cardiovascular disease.[27,28] Women with early menopause before the age of 45, either naturally[28] or surgically induced,[27] are at higher cardiovascular risk compared to women who cease ovarian function later [RR 1.19 (95 CI 1.08–1.31)] and this is mainly due to coronary heart disease mortality [RR1.11 (95% CI: 1.03–1.2)]. The role of high androgens levels in the development of cardiovascular disease cisgendered women is less clear. While it is known that high endogenous testosterone is associated with increased cardiovascular risk factors including increased intimal thickness, increased coronary plaques and increased arterial thickness,[29] an association between androgen levels and cardiovascular events could not be established in a 10-year follow-up study.[30] The complicating factor here is that the commonest cause of hyperandrogenism in females is polycystic ovarian syndrome which may be acting as a confounder.[29]

In cisgendered males, it is known that hypogonadism is also associated with increased mortality.[31] Men who have a testosterone level in the lower tertile have been shown to have a mortality nearly twice that of men with testosterone levels in the upper tertile over eight years (hazard ratio (HR) 1.88; 95% CI: 1.34–2.63; $p < 0.001$).[32] A meta-analysis of hypogonadism in males confirmed that low testosterone and also high oestradiol levels in males are associated with increased cardiovascular disease (HR 0.837(0.823–0.852) for each nmol/L increment of testosterone; $p < 0.0001$) and

(HR 1.002 (1.003–1.004) for each pmol/L increment of E2; $p < 0.0001$).

Physiologically it appears that abnormally low endogenous production of sex steroids of the birth-assigned gender and the increased levels of sex steroid levels of the opposite gender are associated with higher levels of cardiovascular disease.

Cardiovascular risks and exogenous sex steroids therapy (HRT)

Cisgendered females

The data on the effects of exogenous oestrogen therapy on cardiovascular events in females comes mainly from trials looking at postmenopausal HRT. The WHI trial in postmenopausal women was constructed on the premise that giving oestrogen to postmenopausal women would restore their cardiovascular portection;[33] however, the trial demonstrated an increase in cardiovascular events which lead to its premature termination. For all cardiovascular events, hazard ratios were increased at 1.13 (95% CI: 1.02–1.25) for the conjugated equine oestrogen (CEE) + medroxyprogesterone acetate (MPA) arm of the trial. After adjusting for multiple analyses the hazard ratios for stroke, total myocardial infarction (MI), coronary artery intervention and cardiovascular deaths were not increased; however, there was increased risk of thromboembolic events that remained at 2.11 (95% CI: 1.26–3.55).

A subsequent trial looking at the effect of CEE alone in hysterectomised females[34] found the hazard ratio for all cardiovascular events was still increased to 1.11 (95% CI: 1.01–1.22) but this was shown to be age dependent; the hazard ratios for MI increased by decade of age (0.55 for 50–59 years, 0.95 for 60–69 years and 1.24 for 70–79 years). These data suggest that the use of oestrogen without progestin given to females at an earlier age within 10 years of menopause results in the least impact on cardiovascular events.

Further meta-analysis of 23 randomised control trials of women receiving HRT again demonstrated a 32% reduction in cardiovascular events;[35] these data suggest that, providing there is not a significant time without sex steroid exposure, oestrogen HRT can maintain cardiovascular health. Even though high endogenous production of testosterone is associated with increase in markers of cardiovascular risk,[29] the use of therapeutic testosterone replacement in women has not demonstrated any adverse impact on cardiovascular health, suggesting it is safe when doses are given to achieve testosterone values in the female range.[36,37]

Cisgendered males

The treatment of hypogonadism in males with testosterone therapy is associated with varying results with regards to cardiovascular safety. Some have advocated transdermal replacement as a more physiological route.[38] There have been several meta-analyses and reviews on this topic; six out of seven of these did not demonstrate any increase in cardiovascular events. These data have been reviewed in the Lancet with summary estimates demonstrating no significant association between exogenous testosterone and cardiovascular events ranging from [RR 1.07–1.82].[39]

There has, however, been controversy about the use of testosterone in elderly men with three trials suggesting there is an increase in cardiovascular risk.[4–6] In the first trial of 209 elderly men, 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. This trial, however, was criticised as the dose of testosterone used (100 mg topical gel) was extremely high, and it is double a standard hormone replacement dose. In an elderly group of men, it is perhaps not surprising that adverse events occurred. Indeed there was a 3% increase in haematocrit which may have increased plasma viscosity and contributed to this increase in cardiovascular events.[5]

The second study reported that testosterone replacement therapy resulted in an increased risk of MI within 90 days of receiving a testosterone prescription in men ≥65 years old [odds ratio 2.2] and those <65 years with pre-existing heart disease, [odds ratios 2.9].[4]

In the third study, men with hypogonadism who underwent coronary angiography and were replaced with testosterone had an increase in adverse outcomes when using a composite endpoint of myocardial infarction, stroke and death. (HR 1.299 95% CI: 1.04–1.58).[6] This study was, however, criticised as the biological effects of testosterone therapy were not reported and only 1:5 of the testosterone prescriptions were ever filled suggesting the hypogonadism was not corrected.[40]

Other studied contradict these data. Testosterone replacement to physiological levels in hypogonadal men resulted in an improvement in endothelial function and arterial stiffness.[29] An extensive meta-analysis of testosterone therapy for hypogonadism in men did not demonstrate any effect of testosterone therapy on all-cause mortality (OR 1.12 95% CI: 0.7–1.81), risk for MI (OR 1.0.91 95% CI (0.29–2.82)), or need for coronary artery vein grafting (OR 1.35 95% CI (0.26–6.98)), suggesting that on balance testosterone therapy with the aim of replacement to the normal male range is safe.

Transgendered women

Oestrogen therapy and androgen suppression in transgendered females simultaneously has a positive and negative effect on cardiovascular risk factors. The metabolic effects of oestrogen therapy are centred around alteration in liver function and the effects of oestrogen on lipid parameters. There appears to be a decrease in hepatic lipase activity by 64% and of lipoprotein lipase by 23%.[8] Hepatic lipase decreases HDL-cholesterol levels, by catalysing the hydrolysis of triacylglyceride which results in the conversion of lipid-enriched HDL 2 particles to lipid-poor HDL 3 particles; it also increases the formation of small, dense LDL particles both of which are highly atherogenic. Reducing the levels of hepatic lipase may reduce the formation of these atherogenic lipid particles.

Cross-sectional studies, however, suggest that oestrogen has a positive effect on plasma lipids with higher HDL +0.2 mmol/L (6 mg/dl)[41] and 0.16 mmol/L (6 mg/dl)[42] and lower LDL as the LDL-C level was statistically significantly lower in oestrogen treated transgendered female group (5.71 mmol/L; 95% CI: 5.96–5.44 mmol/L; I2 = 0%) (220.3 mg/dL; 95% CI: 230.7–210.0 mg/dL; I2 = 0%).[8] There was no change in other lipid parameters. These studies have small participant numbers making the reliability of the findings uncertain.

The effect of oestrogen treatment in transgendered women has been described in 3 meta-anlyses.[7,9,43] The use of oestrogen therapy in transgendered females showed no statistically significant difference in serum LDL-C, HDL-C, and total cholesterol levels but there was an increase in plasma triglyceride levels after 24 months 0.360 mmol/L; (95% CI: 0.04–0.67 mmol/L) (31.9 mg/dL; 95% CI: 3.9–59.9 mg/dL).[9]

Body composition also changes,[44] there is a significant increase in body weight (+3%; 95% CI: +2% to +5%, $p < 0.001$) and total body fat (+28%; 95% CI: +24% to +32%, $p < 0.001$). At the same time there is a reduction in lean body mass −3% (95% CI: −4% to −2%, $p < 0.001$).[45] Gender affirming hormone therapy has also been shown to increase visceral fat.[46] These changes in body composition would be expected to have a negative impact on cardiovascular risk.

In a study by Elbers et al, employing euglycaemic clamping, insulin sensitivity appeared to be reduced (by 33%) with a commitment increase in insulin levels (by 50%). Fasting glucose however appeared not to be affected.[8] Other studies have demonstrated no change in either fasting insulin levels, HOMA-IR or fasting glucose levels.[43,47,48]

There are differing reports on the effect of gender affirming hormonal therapy in blood pressure in

transgendered females.[24] In one large cohort study of 247 individuals oestrogen had no effect on blood pressure[49] but in another there was a significant increase of systolic blood pressure by 7.2 mmHg and diastolic blood pressure of 5.7 mmHg.[8]

Elevated plasma level of total homocysteine had been shown to be an independent risk factor independent for CVD.[50–52] Total homocysteine levels vary between the sexes; the levels are approximately 10–15% lower in women.[53] Oestrogen therapy in transgendered females reduced plasma homocysteine levels 8.2 mmol/L to 5.7 mmol/L ($p = 0.001$);[54] this effect is independent of the route of administration of oestrogen,[55] This may have a beneficial effect on cardiovascular risks.

Oestrogens alter prothrombotic and inflammatory markers in transgendered women that may have a role in cardiovascular disease. It as has been demonstrated that oral ethinylestradiol in combination with cyproterone acetate but not transdermal 17Beta oestradiol increases CRP[56] and decreases tissue plasminogen activator.[57] Other studies have however shown no effect on CRP[58] and so the impact of oestrogen therapy on prothrombotic changes is unclear. It is of note however that one of the long term outcome studies suggest that the increase in cardiovascular risk was limited to current users of ethinylestradiol[22] and the finding that ethinylestradiol promotes a more prothrombotic mileu would provide a possible explanation for this result.

The current literature demonstrates that oestrogen therapy in transgendered females can result in a mix of changes to physiological parameters. Some increase cardiovascular risk; increased body fat, increased weight, increased visceral fat, reduced lean mass, prothrombotic blood changes, and higher triglyceride. Others decrease cardiovascular risk such as reduced LDL cholesterol and increases plasma homocysteine levels. With studies showing an increased rate of stroke[10,13] and thromboembolism[9,10,13] it is likely that the pro-atherogenic changes predominate.

Transgendered men

There are significant gender differences in lipid parameters, with males having higher total cholesterol, LDL cholesterol and triglyceride, with lower plasma HDL cholesterol. As expected, testosterone therapy in transmen adversely alters their lipid parameters. A recent meta-analysis of the available data demonstrated there was no change in total cholesterol or LDL cholesterol but there was a minor increase in triglyceride (0.35 [CI 0.09–0.62] mmol/L) and a decrease in plasma HDL levels(−0.73[CI −0.3 to 0.02] mmol/L), both of which are pro-atherogenic.[7] A more recent meta-analysis showed that the changes in lipid parameters

were progressive with time over 24 months so that by 24 months of testosterone therapy TG levels were higher (+0.24 mmol/L; 95% CI: 0–0.48 mmol/L) (+21.4 mg/dL; 95% CI: 0.1–42.6 mg/dL) compared with baseline; the serum LDL-C level showed a statistically significant increase (+0.46 mg/dL; 95% CI: 0.1–0.83 mg/dL) (+17.8 mg/dL; 95% CI: 3.5–32.1 mg/dL). HDL-C level decreased significantly (−0.21 mg/dL; 95% CI: −0.34 to −0.1 mg/dL) (−8.5 mg/dL; 95% CI: −13.0 to −3.9 mg/dL). Total serum cholesterol level did not show a statistically significant change.

With regards to body composition, there is an increase in weight in transgendered men treated with testosterone of +3% (95% CI: 2%; 4%, $p < 0.001$) but this is accompanied by a decrease in total body fat of −9% (95% CI: −12%; −7%, $p < 0.001$) and an increase in total lean body mass of +10% (95% CI: 9%; 11%, $p < 0.001$).[45] On balance, this would be a positive change for metabolic risk.

In transgendered men, testosterone therapy has no effect on fasting glucose, fasting insulin or glucose utilisation.[8] Studies are contradictory with regards to testosterone's effect on blood pressure in transgendered males. Six studies assessed effects testosterone therapy on blood pressure levels in transgendered men.[59] In one study, there was an increase in both systolic and diastolic blood pressure;[60] in two studies there was an increase only in systolic blood pressure[47,61] and in two others no significant changes were found.[41,49] In another study, there was a decrease in systolic and diastolic blood pressure levels.[62]

Testosterone therapy increases plasma homocysteine levels in transgendered men[54] 7.7 mmol/L to 9.0 mmol/L ($p < 0.005$) which could have a negative impact on cardiovascular risk.

It is interesting that these changes in lipid profile do not appear to translate into an alteration in cardiovascular risk, as there is no increase in cardiovascular mortality in treated transmen; indeed one study suggested the MI rate is approximately one-third of that expected in the general male population.[63] These findings have been confirmed in long-term follow-up studies where the standard mortality ratio for transmen is not different from the general population.[22]

Other risk factors

The metabolic factors for cardiovascular disease other risk factors can have a significant effect in the transgendered population.

Smoking

Smoking is an important risk factor for cardiovascular events and tobacco use has been demonstrated to be high in the transgendered population. The incidence of smoking in the reports series varies from 15%[10] to 63.5%[64] in transgendered women and 18%[10] to 74.4%[64] in transgendered men. Smoking is such a powerful co-factor in cardiovascular disease that it may represent a considerable confounder when looking at the cardiovascular risk in transgendered people.

It is interesting that the rate of smoking in transgendered men is higher than that of transgendered women and yet cardiovascular mortality does not seem to be impacted. In two large series, the rates of MI and stroke in transgendered men are not higher than either birth-assigned females or birth-assigned males.[10,13] In another series of 816 transgendered people, the MI rate for transgendered men was one-third that of the general population (SIR 0.05 [0.24–0.91]),[63] despite a high rate of tobacco use at 43–46%.[13] More recently, however, a large community-based study of 1.4 million people suggests that smoking rates in transgendered men and women were higher than the cisgendered population (smoking rate transgendered men 19.3%, transgendered women 20.3%, cisgendered men 18.6%, cisgendered women 14.4%) and here MI rates were higher in transgendered men compared to cisgendered men (OR 2.53 95% CI: 1.14–5.63) and cisgendered women (OR 4.90 95% CI: 2.21–10.90).

HIV infection

The incidence of HIV infection in the transgendered female population appears to be increased compared to the general population.[63] It is has been estimated that just under a third of transgendered women in the USA may be seropositive.[65] A systematic review which looked at 39 studies suggested a global HIV prevalence rate of 19.1% in transgendered women.[66] Interestingly, in this review a much higher HIV burden was found in transgendered women of colour, Hispanic 49.6% and African American transgendered women 48.1%.compared to Caucasian transgendered women at 3.5%. As ethnic origin is a cardiovascular risk factor per se, this could mean transgendered women living with HIV have a very high cardiovascular risk.

The association between HIV infection and cardiovascular disease is caused by a combination of traditional risk (e.g. smoking, diabetes, lipid abnormalities), disease-specific risk factors (e.g. chronic inflammatory response and lipoprotein-a levels), the effect of antiretroviral agents, the virus itself and consequences of the immune response. Coronary artery disease is one of the leading causes of death in HIV-infected patients.[67]

One study examined the incidence of coronary risk factors in transgendered females compared to a cisgendered male control group and found that there were no

difference in the incidence of cardiovascular risk factors between the groups.[68] They did, however, note that the transgendered female group did have suboptimal HIV control. This heightened immune activation may be a mechanism by which accelerated cardiovascular disease can occur.

None of the outcome studies in transgendered people so far have commented on the incidence of HIV seropositivity in the reported populations and so cannot be excluded as a cofactor increasing cardiovascular disease incidence.

Stress

Psychological distress is a well-established CVD risk factor, as it is believed to result in atherosclerosis by immune dysfunction and maladaptive metabolic responses.[69] Transgendered people are known to suffer from minority stress.[70] Stigmatisation which is experienced by people in this community enhances distress via unhealthy coping mechanisms such as concealment.[70]

In the US transgender survey, 39% of respondents reported severe psychological distress. This figure is eight times higher than the general population.[70] It known that stressful events, chronic stress or repeated acute stress places people at a higher cardiovascular risk.[69] Undertaking treatment for gender dysphoria has been shown to successfully reduce stress, improve quality of life and also to reduce tobacco use.[71,72] These measures may obviate some of the cardiovascular risk associated with gender affirming hormonal therapy in the transgendered population.

Cardiovascular outcomes in transgendered people

Cardiovascular mortality

Long-term outcome studies have demonstrated that mortality is increased in the transgendered population.[21,22] Although the major causes of death in these studies appeared to be from suicide, complications related to HIV and malignancies cardiovascular risk was also raised in both these studies.[21,22] The first study was a population-based matched cohort study in Sweden including 324 participants with an average follow-up of 11.4 years and it demonstrates a HR of 2.5 (1.2–5.3) for death by cardiovascular disease. This study is of limited use in dissecting the cause of this mortality, as it was not stratified for gender, hormone type used or smoking status. A single-centre cohort observational study of 996 participants with an average follow-up of 18.5 years, reported that the standard mortality ratio was only raised in the transgendered

female population (SMR 1.51(95% CI: 1.47–1.55) and not the transgendered male population (SMR 1.12 (95% CI: 0.87–1.42). These data suggest that increased cardiovascular mortality exist in the transgendered population. However, this increase in cardiovascular morbidity is limited to the transgendered female population.

Myocardial infarction (MI)

In the Asscheman cohort study, ischemic heart disease was the cause of death in 18 subjects (SMR 1.64; 95% CI: 1.43–1.87).[22] These findings have been repeated in the USA with data from the Behavioural Risk Factor Surveillance System, with a population of 691 transgendered people. The adjusted odds ratio for MI was increased to 1.82 (95% CI: 1.22–2.72) but the study did not stratify the data by birth assigned gender.[11]

In contrast, other studies have not shown an increase in myocardial infarction; in a population of 352 transgendered people with 7.4 years of follow-up, again there was no significant increase in the incidence of MI compared to control men, although the rate was increased compared to control women (18.7/1000 (compared to 12.5/1000 men p NS and 0/1000 women $p = 0.001$). In another shorter study, the rate of MI was half that expected compared to birth assigned males (SIR 0.5 (95% CI: 0.24–0.91)).

A large electronic record cohort study of 4960 transgendered people with four years of follow-up demonstrated no increase in MI compared to reference males or females (HR 1.0 (95% CI: 0.3–3.2 compared to males; HR 2.4 95% CI: 0.6–9.4)).

Similar findings occurred in a large cohort study in Holland of 6793 participants with mean follow-up of 9.07 years. This study reported SIR for MI of 0.79 (95% CI: 0.57–1.11 compared to cisgendered males) and 2.64 (95% CI: 1.81–3.72 compared to cisgendered females $p < 0.01$).[13]

A very recent study from the USA looked at a very large population sample of 1,842,439 which included 340,365 transgendered women. This study demonstrated that there was a significantly increased rate of MI in transgendered women compared to cisgendered women (7.8% vs. 3.1%; $p < 0.01$) and cisgendered men (7.8% vs. 5.6%; $p < 0.01$). However, after adjusting for age, diabetes mellitus, chronic kidney disease, smoking, hypertension, hypercholesterolemia, and exercise, transgendered women only had a significantly increased risk of MI compared to cisgendered females (odds ratio [OR], 2.56; 95% CI: 1.78–3.68; $p < 0.01$) but not cisgendered men.[12]

For transgendered men, MI rates were higher when compared to cisgendered women (7.2% compared to 3.1%; $p < 0.010$), but there was no difference when

compared to cisgendered men (7.2% compared to 5.6%; $p = 0.30$). After adjustment for cardiovascular risk factors, however, the study demonstrated that transgendered men had an increased risk for MI compared to both cisgendered populations (OR 2.53 95% CI: 1.14–5.63 compared to cisgendered men; OR 4.90 95% CI: 2.21–10.90 compared to cisgendered women).[12]

This finding is in contrast with the findings of the other studies looking at MI in transgendered females where the MI rate is lower than the cisgendered male[63] population and also for transgendered men where studies have shown the MI rate is either lower or similar to the cisgendered male population.[10,23,63] Although there was a large study population, the investigators used self-reporting of trans status to identify the transgendered population in the study rather than a diagnostic assessment as part of a gender dysphoria assessment and treatment programme which has been used in the other reported series. This may mean that the two populations differ significantly with regards to access to gender affirming hormone therapy. Indeed this study could not comment on whether the individuals were taking gender affirming hormonal therapy to treat their gender dysphoria. It may therefore be that case that taking gender affirming hormonal therapy to treat gender dysphoria has a positive effect on cardiovascular outcomes in transgendered people as MI rates are higher in a self-reported transgendered population compared to those in a treatment and assessment programme.

This study emphasises the importance of cardiovascular co-morbidities such as smoking, reduced exercise, diabetes and non-Caucasian ethnic origin, all of which were seen in higher numbers in the transgendered population.

The balance of evidence appears to support the finding that gender affirming hormonal therapy in transgendered females may reduce MI rate but not to the level of cisgendered women. In transgendered men, the risk of MI is higher than the cisgendered female population but probably no higher than the cisgendered male population.

Stroke

Five studies have reported on the incidence of stroke in the transgendered population. In the Asscheman study, five people died of stroke and they reported a non-significant SMR of 1.26 (95% CI: 0.93–1.64).[73] Similarly, Wierckx reported an incidence of stroke of 23.4/1000 which was significantly higher than control men (9.4/1000; $p = 0.03$) but not significantly different when compared to control females (14.9/1000).[44] In the USA, Meyer reported a reduced stroke incidence in the transgendered population OR 0.65 (95% CI: 0.43–0.99).[11]

Two larger studies, however, suggest that the incidence of stroke was increased. Nota et al. reported a significantly increased rate of stroke in transgendered females with a SIR 1.8 (95% CI: 1.23–2.56 compared to cisgendered males) and 2.42 (95% CI: 1.65–3.42 compared to cisgendered females).[74] In the Gatahun paper, however, overall stroke risk was not increased compared with reference males (HR 1.2 995% CI: 0.9–17) but increased compared with reference females (HR 1.9 (95% CI: 1.3–2.6)).[10] In a subgroup analysis looking at those that commenced oestrogen therapy during follow-up, the incidence of stroke appeared to increase after six years of treatment compared to both reference males and reference females.[10]

These data give conflicting results with regards to stroke rates in the transgendered female population. Most of the studies suggest that stroke rates are between that seen in cisgendered males and cisgendered females. In contrast, one large cohort study suggests that increased stroke incidence does not become apparent until six years of exposure.[10] However, a moderately sized study a with follow-up duration of three times this duration, refuted this finding.[22]

Thromboembolism

There is strong evidence that oestrogen increases thromboembolic events in cisgendered women. The WHI study confirmed that DVT incidence was increased (HR 1.87 (95% CI: 1.37–2.54) for the CEE + MPA trial and 1.48 (95% CI: 1.06–2.07) and pulmonary embolus (HR 1.98 (95% CI: 1.36–2.87).[75] In the oestrogen only arm of the trial, this translated to an extra 7–12 deep vein thromboses/10,000 person-years.[76] A Cochrane review found that hormone replacement therapy was associated with an increased risk of venous thromboembolism in all populations of post-menopausal women: whether HRT started <10 years post menopause [RR 1.74 (95% CI: 1.11–2.73)], >10 years post 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)].[77] The increased risk represents 5–12 additional cases of venous thromboembolism (VTE) per 1000 people.[77] The increased risk was largely driven by women on combination hormone therapy.

The route of oestrogen delivery, and type of progestin used in HRT also have an influence on thromboembolic risk. In a case-control study of post-menopausal women, the rate of VTE was raised in current oral oestradiol hormone therapy users,[78] (adjusted OR 4.2 (95% CI: 1.5–11.6) but this was not seen in transdermal oestrogen (OR 0.9 (95% CI: 0.4–2.1).

Non-pregnane progestins (nomegestrol acetate and promegestone) were associated with increased VTE of OR 3.9 (95% CI: 1.5–10.0) whereas no differences were noted with micronised progesterone or pregnane derivatives (medroxyprogesterone acetate, dydrogesterone, medrogestone, chlormadinone acetate and cyproterone acetate).

In younger women, although stroke and MI risk is low, that risk is increased by the use of the synthetic oestrogen ethinylestradiol. The absolute risk is dose dependant, with oral contraceptives that contained ethinylestradiol at a dose of 20 mg/day increasing the absolute risk by 0.9–1.7 fold and with those containing ethinylestradiol at a dose of 30–40 mg/day by a factor of 1.3–2.3.[79] As transgendered women usually take doses 2–5 times higher than this, and safer alternatives are now available, the use of ethinylestradiol is best avoided.

Another important cofactor is smoking. Smoking by women taking the oral contraceptive pill increases the risk of stroke and DVT.[80] The incidence appears to be dose related, with the higher dose pill (80 μg oestrogen) having a higher incidence of DVT. The doses of oestrogen used in the contraceptive pill are approximately half those used for feminisation in the transgendered female population, and so it is strongly recommended that patients stop smoking prior to commencing oestrogen therapy to minimise the risk of DVT. Other studies of the contraceptive pill have failed to demonstrate this association, but these studies used combined contraceptive pills with much lower oestrogen doses which may explain the different findings.[80–82]

There have been reports of a possible link between testosterone replacement therapy use and increased VTE risk in men;[83] however, these studies were criticised for including data on events such as avascular necrosis of the femoral head which are not classically viewed as VTE events. Larger epidemiological studies have demonstrated that there is no link between testosterone therapy and thromboembolism risk, and these data were summarised in a recent meta-analysis (OR 1.41 (95% CI: 0.96–2.27)).[84]

In transgendered women, initial studies suggested that gender affirming hormone therapy use was associated with a 45-fold increase risk of VTE when ethinylestradiol and cyproterone acetate was used. This appeared to be age related as women over 40 years old had a deep venous thrombosis rate of 12% and those under 40 only 2.1%.[73] By changing to transdermal oestrogen after the age of 45 years in transgendered women, this group reduced the rate of DVT from 12% to 2.6% in their clinic population.[63] The majority of these incidents occur during the first two years of treatment. There is, however, an on-going risk of 0.4% per year.[63]

A recent a meta-analysis of 1767 individuals on oestrogen therapy found VTE rates of 0–5% in 10 studies with variable durations of follow-up.[9] The rate of VTE was not increased in transgendered men.

Since that meta-analysis, two new large trials have reported VTE rates. Nota et al. have reported significantly increased rate of VTE in transgendered women with a SIR of 4.55 (95% CI: 3.59–5.69 compared to cisgendered males) and 5.52 (95% CI: 4.36–6.9 compared to cisgendered females).[13] There was no increase in VTE in transgendered men a SIR 0.36 (95% CI: 0.06–1.19 compared to cisgendered males) and 0.41 (95% CI: 0.07–1.37 compared to cisgendered females). In the large electronic data base cohort study reported by Getahun et al., the risk for VTE was increased in the transgendered female population – HR 1.9 (95% CI: 1.4–2.7) compared to reference males and 2.0 (95% CI: 1.4–2.8) compared to reference females.[10] This study, in contrast to all the previously reported studies, report suggested that VTE risk increases after two years of oestrogen therapy[10] In the earlier literature, the majority of VTE events occurred in the first two years of treatment,[9,13] and further studies are needed to examine the temporal relationship between thromboembolic events sand gender affirming hormone therapy in transgendered women. In the Getahun et al. study, again there was no increase in VTE risk in transgendered males.[10] These new studies suggest a much lower risk of VTE which is approximately 2-fold higher than the control populations compared to the previously reported 20-fold increased risk.

The thromboembolic risk is modulated by several factors such as the oestrogen type, the route of delivery and the co-administered androgen-lowering medications. Ethinylestradiol alters the plasma concentrations of protein S, C and prothrombin, which results in a procoagulant haemostatic profile in transgendered women. Oral ethinylestradiol 100 mcg daily in combination with cyproterone acetate 100 mg/day caused a significant increase in activated protein C (APC) resistance (nAPCsr 1.2 ± 0.8 to $4.1 U \pm 1.1$); however, transdermal oestradiol 100 mcg twice per week and cyproterone acetate 100 mg or cyproterone acetate monotherapy had a minor effect ($1.3 U \pm 0.6$ to $2.0 U \pm 2.0$ and 1.4 ± 0.6 to 1.8 ± 0.9, respectively).[85] Ethinylestradiol and cyproterone acetate also decreased the coagulation inhibitor Protein S. These changes were not observed when either transdermal oestrogen or oral oestrogen valerate was used.[85] There were no thromboembolic events seen in either group, but this was a short-term study. The presumption from this study was that the route of administration of oestrogen was important but other studies have challenged this view, suggesting the type of oestrogen and not route of administration may be more

important. A study demonstrated that the incidence of VTE in a population of 330 transwomen was 0.6% for those treated with oral oestradiol in doses of up to 10 mg daily but the incidence of VTE was eight-fold higher in those treated with CEE. These data would support the hypothesis that oestrogen type not route of administration has more impact on DVT rate in transwomen.[86] This has also been recognised in contraceptive practice where the prothrombotic effect of ethinylestradiol has been ascribed to its molecular structure rather than to the first-pass liver metabolism creating thrombogenic oestrogen breakdown products.[87]

Hormonal factors in cardiovascular disease in transgendered people

We know from long-term outcome studies that the use of ethinylestradiol in transwomen is associated with increased cardiovascular risk (adjusted OR 3.64 (95% CI: 1052–8.73) and this risk is not seen in past users of ethinylestradiol, 17β-oestradiol preparations or conjugated equine oestrogen (CEE).[22] The problem with the meta-analyses so far is that few of the transgendered women were treated with 17β-oestradiol, the majority were treated with either ethinylestradiol or CEE, and only 7% were on 17β-oestradiol and GnRH analogues. This is an area where further research is needed to characterise the effects of 17β-oestradiol preparations rather than ethinylestradiol or CEE on lipid parameters.[7]

In modern practice, the majority of clinics internationally have moved to using 17β-oestradiol rather than other oestrogen preparations when providing gender affirming hormonal therapy for transgendered women and this may have contributed to the reduced VTE risk observed in the newer larger studies. This change in clinical practice, however, acts as a confounding factor because the long-term follow-up studies include individuals treated with both types of oestrogen regimen[13,21,22] making the interpretation of long-term data difficult in this population.

Smoking is also a significant confounder in these studies. We know from the combined contraceptive pill studies that the incidence of VTE is increased in smokers by approximately two-fold, and smoking in combination with obesity increases this risk to nine-fold.[88] An important feature of the protocol used in the largest UK clinics is that the client must stop smoking in order to receive high-dose oestrogen,[89] which is an attempt to reduce the VTE risk of this patient population. The incidence of smoking in the recent Dutch long-term study is estimated at 43–46%[13] whereas the incidence of smoking at the time of a cardiovascular event in the Getahun et al. report was 20%.[10]

As smoking is a strong cofactor in both VTE and cardiovascular events in transgendered people,[23] these different levels of tobacco use across cohorts may have a significant impact on the rates of cardiovascular events making the interpretation of results difficult. In UK practice, individuals strongly are encouraged to cease smoking before hormone therapy is initiated.[89]

Finally, the method used for testosterone suppression may have an influence on the rate of cardiovascular disease. In Europe, cyproterone acetate is the mainstay of androgen suppression. This antiandrogenic progestin may increase the risk of thromboembolism when given in combination with oestrogen. We know from the cisgendered female population that oestrogen progestin HRT is more thrombogenic than oestrogen alone HRT.[75]

In the UK, GnRH analogues form the mainstay of androgen suppression.[90] In Europe because of the expense of these medications, it is more usual to use cyproterone acetate for androgen suppression. One study has made a direct comparison between cyproterone acetate and leuprolide for androgen suppression in combination with transdermal 17β-oestradiol. Leuprolide was equally effective at inducing androgen suppression but it was less likely to induce hyperprolactinaemia. More interestingly 17β-oestradiol and leuprolide therapy increased HDL cholesterol (+0.2 ±0.5 mmol/L) whereas cyproterone acetate and 17β-oestradiol therapy decreased HDL-cholesterol (−0.2 ± 0.3 mmol/L).[91] This may be important in the development of cardiovascular disease which may alter the rates.

In transgendered men, it is interesting that adverse effects of androgens on lipid profile do not appear to translate into an alteration in cardiovascular risk. There is no increase in cardiovascular mortality in testosterone-treated transgendered men; indeed the MI rate is between one-third expected in the cisgendered male population[63] and expected male gender population norms.[13] These findings have been confirmed in long-term follow-up studies where the standard mortality ratio for transmen is not different from the general population.[22] These data suggest that cardiovascular risk factors have less of an impact on cardiovascular disease in transgendered men compared to cisgendered men. The mechanism for this would be interesting to explore in future studies looking at the impact of the protective oestrogenic environment in early life on future cardiovascular risk.

Conclusion

Current evidence suggests that hormonal therapy for transgendered women decreases or is neutral regarding MI. There is an increased incidence of VTE, but newer

studies suggest that the risk is significantly lower than previously described. The studies available looking at more modern regimens are, however, scarce and currently have short-term follow-up duration. Therefore, we do not yet know whether these treatment regimens will improve cardiovascular risk. Stroke risk may be increased and further studies are required to clarify the long-term cardiovascular risks of gender affirming hormonal therapy in transgendered women.

For transgendered men, there appears to be an adverse effect on lipid parameters, but this does not translate into an increased risk of cardiovascular disease. The younger age of transgendered men in the studies so far may mean that a longer follow-up is needed to assess whether there is truly an increased cardiovascular risk.

In all transgendered people, cardiovascular risk factor interventions such as smoking cessation, weight management and treatment of co-morbid conditions are important in optimising cardiovascular health.

The effects of gender affirming hormonal therapy on transgendered people's cardiovascular health are difficult to interpret due to the variety of hormone regimens used, the relative brevity of the periods of observation and the influence of confounding factors. There is still need for further research in this area.

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ORCID iD

Leighton J Seal https://orcid.org/0000-0001-8151-8634

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