

# Transgender health

## Managing cardiovascular risk in adults who use gender-affirming hormone therapy

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Cardiovascular risk appears to be higher in transgender individuals who are receiving gender-affirming hormone therapy; however, it remains unclear how much of this specifically relates to hormone therapy. Understanding the impact of gender-affirming hormone therapy on specific factors, including venous thromboembolic risk, changes in body composition, insulin resistance, lipid levels and blood pressure, can help mitigate potential cardiovascular risk in the transgender population.

Transgender individuals experience incongruence between the sex assigned to them at birth and their deeply held sense of gender identity. Many transgender individuals use gender-affirming hormone therapy to align their body with their gender identity. Use of masculinising hormone therapy (testosterone) in transgender men and feminising hormone therapy (estradiol and antiandrogen agents) in transgender women are both associated with improvements in psychological outcomes and quality of life.<sup>1</sup>

Gender-affirming hormone therapy is usually continued lifelong and understanding any potential adverse effects is important to try to mitigate any potential risks. Monitoring and longer-term management of the use of gender-affirming hormone therapy largely takes place in the general practice setting and a practical approach to monitoring and optimising cardiovascular risk in transgender adults is needed. An individual considered to be at high risk should be referred for more specialised cardiovascular assessment.

MedicineToday 2024; 25(6 Suppl): 30-32

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### KEY POINTS

- Transgender adults who are using gender-affirming therapy have an almost twofold higher mortality rate compared with the general population.
- Transgender women are more likely to die from cardiovascular disease and have higher rates of venous thromboembolic disease and stroke compared with the general population.
- Risk of mortality from cardiovascular disease in transgender men is inconclusive, with different studies showing contrasting results.
- Modern gender-affirming hormone therapy formulations may confer a lower risk of cardiovascular disease than the regimens historically studied.
- Ethinylestradiol and conjugated estrogens are not recommended for transgender women. Transdermal, rather than oral, estradiol is preferred for transgender women at higher cardiovascular risk.
- Smoking cessation, regular exercise, dietary interventions and maintaining a healthy weight range are recommended.
- Monitoring blood pressure, weight, body mass index, lipid profile and blood glucose level are recommended annually.

### Overall cardiovascular risk

Cardiovascular risk is influenced by genetic and environmental factors. Sex hormone exposure is known to play a significant role, as it influences body composition, insulin resistance and lipid profile. The relations between sex hormones and cardiovascular risk is complex, and it is currently unclear exactly how much of this sex hormone-related risk is assumed or mitigated while taking gender-affirming hormone therapy. In addition, transgender individuals experience significant minority stress and higher socioeconomic disadvantage. As a community, they face higher rates of discrimination, and have significant barriers when accessing healthcare, which are all likely to negatively impact cardiovascular risk.

Trans health research is an emerging field and, as such, our understanding of cardiovascular risk in transgender populations is limited. Ongoing studies typically include a heterogeneity of participants often taking varying hormone formulations, and much of the published data comes from retrospective cohort studies that include participants on hormone therapy regimens no longer used nor recommended.

In 2021, a large Dutch retrospective cohort study found that transgender adults using gender-affirming hormone therapy had an approximate twofold higher mortality rate than the general population. Transgender women had a higher risk of death compared with both general population men and women due to cardiovascular disease, HIV-related disease, lung cancer and suicide.<sup>2</sup> Transgender women were also 2.6 times more likely to die from cardiovascular disease compared with general population women (95% confidence interval [CI], 1.9–3.4) and 1.4 times more likely compared with general population men (95% CI, 1.0–1.8). Death from myocardial infarction was similar compared with general population men but 2.6 times higher (95% CI, 1.7–4.5) compared with general population women.<sup>2</sup>

A large 2019 retrospective cohort study (using data collected between 1972 and 2015) showed that transgender women had a higher rate of venous thromboembolic disease and stroke.<sup>3</sup> A major limitation of the study was the inclusion of data from participants on hormone therapy regimens that are no longer recommended, such as ethinylestradiol and conjugated estrogen.

The previously mentioned 2021 Dutch study found no significant increase in mortality from cardiovascular disease, including myocardial infarction, in transgender men compared with either general population men or women; however, transgender men had a higher risk of death from non-natural causes compared with general population women.<sup>2</sup> By comparison, a large 2019 retrospective cohort study showed that transgender men had similar rates of myocardial infarction to general population men, but higher rates than general population women.<sup>3</sup>

### **Venous thromboembolic risk**

Studies evaluating risks associated with gender-affirming hormone treatment showed that transgender women taking traditionally used formulations, such as ethinylestradiol 100mcg daily and cyproterone acetate 100 mg daily, had an

extremely high venous thromboembolic risk (6.3%).<sup>4</sup> Conjugated equine estrogens have also been associated with a high risk of venous thromboembolism (VTE) and are no longer recommended.<sup>5</sup> In contrast, modern gender-affirming hormone therapy regimens involving oral or transdermal estradiol have a lower risk of VTE, with recent observational data suggesting the risk is between 0 and 2%.<sup>6</sup> Transdermal estradiol may confer the lowest risk of VTE, based on studies in menopausal women using hormone therapy.<sup>7</sup> It is unclear if antiandrogen agents have an independent effect on cardiovascular risk.

Transgender men using intramuscular testosterone had a higher rate of polycythaemia than those taking transdermal preparations, which may contribute to thromboembolic risk.

### **Body composition and insulin resistance**

A potential explanation for higher cardiovascular risk in transgender adults is the large body composition changes that occur during gender-affirming hormone therapy. Although an individual's overall weight may change only by a few kilograms, there are large fluctuations in lean and fat mass. Body composition studies in transgender women show higher overall fat mass (median, +9.8kg), higher gynoid distribution of fat (hip and thigh) and lower lean mass (median, -6.9kg). These changes were associated with higher levels of markers of insulin resistance. Although transgender women had more gynoid fat, the central android fat mass was not actually lower, which, along with the lower lean mass, likely explained the insulin resistance in this group.<sup>8</sup>

Transgender men had significantly higher lean mass (median, +7.8 kg) as well as a higher android to gynoid fat ratio; however, no significant differences in insulin resistance were observed. This may be because there was no overall increase in fat mass compared with control women (who were not taking gender-affirming hormone therapy), with the increase in lean mass conferring some protection.<sup>8</sup>

### **Lipids**

In transgender women taking feminising hormone therapy, a meta-analysis of 29 studies (n=323) showed no significant differences in total, LDL or HDL cholesterol levels. Triglyceride levels, however, were higher than baseline after 24 months using hormone therapy.<sup>9</sup> Two large cohort studies and one prospective study of participants taking masculinising hormone therapy observed higher total LDL cholesterol and triglyceride levels, as well as lower protective HDL cholesterol.<sup>10-12</sup>

### **Blood pressure**

Studies of feminising and masculinising hormone therapy regimens show conflicting results regarding blood pressure, with some studies showing an increase and others showing no increase in blood pressure in people taking these hormone therapies.<sup>10,11,13,14</sup> Therefore, overall blood pressure is not thought to be significantly affected by gender-affirming hormone therapy regimens. Nonetheless, hypertension is common in all populations and a standard approach to prevention and management is important.

### **Other factors**

Other factors, such as smoking, diet and exercise, may also affect cardiovascular risk, but these factors have not yet been extensively studied in transgender populations. Minority stress, such as gender-based discrimination, violence and structural stressors, may also contribute to social determinants of health.

### **Monitoring cardiovascular risk**

Before a person commences gender-affirming hormone therapy, performing a full set of baseline blood tests is recommended, including full blood examination, liver function tests and electrolyte, fasting lipid and glucose levels, as well as estradiol and total testosterone levels.<sup>15</sup> In addition, blood pressure and weight should be checked at baseline and rechecked at least annually.<sup>15</sup> More frequent blood testing is usually performed during the first year

of gender-affirming hormone therapy but longer term, monitoring fasting glucose and lipid levels at least once every 12 months is recommended.<sup>15</sup>

When monitoring biochemistry results in transgender patients, using the reference range of the affirmed gender is generally recommended (for example, the male reference range should be used when interpreting blood tests in a transgender man). An exception is high-sensitivity cardiac troponin testing, as it appears that little cardiac remodelling or change in cardiac size occurs, even with high-dose testosterone concentrations. Therefore, reference range that correlates to presumed sex at birth should instead be used when interpreting high-sensitive cardiac troponin levels (i.e. the female reference range should be used in a transgender man), and taking serial measurements can be helpful.<sup>16</sup>

### A practical approach to cardiovascular risk prevention

It is prudent to encourage smoking cessation, an active lifestyle and a healthy diet in all patients. Blood pressure should be checked routinely, and weight and body mass index monitored at least annually.

In transgender women, transdermal preparations of estradiol are generally preferred, particularly in those aged over 45 years or with any additional risk factor for VTE such as smoking, diabetes or obesity.<sup>15</sup> For those at very high risk of VTE (such as a prior pulmonary embolus), anticoagulation therapy may be appropriate. Serum estradiol should be monitored to prevent supratherapeutic levels, and ethinylestradiol and conjugated estrogens should not be used.

In transgender men taking testosterone, haematocrit level should be monitored and ideally remain below 0.5L/L. If polycythemia is present, lowering the dose of testosterone or swapping from an intramuscular to a transdermal testosterone preparation

can be useful in addition to smoking cessation.

### Conclusion

With the limited data available to date, transgender individuals appear to have a higher cardiovascular risk than the general population. Modern formulations may confer a lower risk of cardiovascular disease than the regimens historically studied. Monitoring cardiovascular risk is performed through baseline and annual blood tests, as well as physical examination (blood pressure, weight, body mass index). Individuals should be counselled on what is known about cardiovascular risk and the contributing factors to that primary prevention strategies can be implemented. Smoking cessation, regular exercise and a healthy diet are recommended. Insulin resistance, lipid profile and blood pressure should be optimised. When investigating high sensitivity troponin levels, using the reference range relating to sex presumed at birth is recommended. To accurately understand cardiovascular risk in transgender adults, additional research that evaluates modern hormone therapy regimens while also controlling for potential confounding factors (such as smoking and minority stress) are needed. **MT**

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COMPETING INTERESTS: None.