# Reviews

# Effects of Gender-Affirming Hormones on Lipid, Metabolic, and Cardiac Surrogate Blood Markers in Transgender Persons

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**BACKGROUND:** Gender-affirming hormonal therapy consists of testosterone in transgender men and estrogens and antiandrogens in transgender women. Research has concluded that gender-affirming therapy generally leads to high satisfaction rates, increased quality of life, and higher psychological well-being. However, given the higher incidence of cardiometabolic morbidity and mortality in cisgender men compared with cisgender women, concerns about the cardiometabolic risk of androgen therapy have been raised.

**CONTENT:** A literature research was conducted on PubMed, Embase, and Scopus, searching for relevant articles on the effects of gender-affirming hormone therapy on cardiometabolic risk and thrombosis. After screening 734 abstracts, 77 full text articles were retained, of which 11 were review articles.

**SUMMARY:** Studies describing a higher risk for cardiometabolic and thromboembolic morbidity and/or mortality in transgender women (but not transgender men) mainly covered data on transgender women using the now obsolete ethinyl estradiol and, therefore, are no longer valid. Currently, most of the available literature on transgender people adhering to standard treatment regimens consists of retrospective cohort studies of insufficient follow-up duration. When assessing markers of cardiometabolic disease, the available literature is inconclusive, which may be ascribed to relatively short follow-up duration and small sample size. The importance of ongoing large-scale prospective studies/registries and of optimal management of conventional risk factors cannot be overemphasized.

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Transgender people are persons whose gender identity differs from their birth-assigned sex. When associated with distress or impairment in social, educational, or other important areas of functioning, gender dysphoria may occur. Although this review focuses mainly on feminizing and masculinizing gender-affirming hormone therapy (HT)[5], "transgender" is an umbrella term referring to a spectrum of gender identities and may include people living with gender incongruence and not searching a transition, those making a social transition only without medical needs, and/or gender-nonconforming persons. These subgroups are often not included in studies and, therefore, are underrepresented in the current review. Population-based questionnaire-generated estimates for the prevalence of gender incongruence range from 0.5% to 1.3% for birth-assigned males and 0.4% to 1.2% for birth-assigned females (1).

The number of transgender persons seeking gender-affirming care is increasing (2), although access to healthcare remains precarious (3). Because of stigma and fear of medicalization, transgender persons may encounter barriers when accessing healthcare (4). Transgender care is currently not a strong part of the medical curriculum (5), which may lead to miscommunication, misinformation, not referring trans persons to the appropriate care providers, postponing necessary healthcare, uncontrolled hormone use, and self-performed gender-affirming surgery (6). Therefore, it is important for healthcare workers in both specialty and primary care to get acquainted with

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[5] Nonstandard abbreviations: HT, hormonal therapy; TW, transgender women; EE, ethinyl estradiol; VTE, venous thromboembolism; CVD, cardiovascular disease; EV, estradiol valerate; GnRH, gonadotropin-releasing hormone agonist; TM, transgender men; PCOS, polycystic ovary syndrome; T2DM, type 2 diabetes mellitus; HRT, hormone replacement therapy; RR, relative risk; CEE, conjugated equine estrogen; BMI, body mass index; WHR, waist–hip ratio; aPTT, activated partial thromboplastin time; PTT, partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio; aHR, adjusted hazard ratio; TIA, transient ischemic attack; SIR, standardized incidence ratio; DVT, deep venous thrombosis.

the needs of transgender persons and to understand the impact on morbidity and mortality.

## Gender-Affirming HT

In transgender women (TW), gender-affirming HT consists of estrogens and antiandrogen agents. Before 2003, the main estrogen agent used in the US was conjugated equine estradiol, whereas in Europe, ethinyl estradiol (EE) was more frequently prescribed to TW. However, epidemiological studies revealed an increased risk for venous thromboembolism (VTE) and cardiovascular disease (CVD) (7), which has led to most clinics abandoning EE for oral [estradiol valerate (EV)], cutaneous (estradiol patches or estradiol gel), or intramuscular 17-$\beta$ estradiol (EV or cypionate) aimed at cisgender female reference ranges (8). Antiandrogen therapy [spironolactone, cyproterone acetate, or gonadotropin-releasing hormone (GnRH) agonists] is usually added to reduce endogenous testosterone concentrations to concentrations found in cisgender women (8).

In transgender men (TM), HT consists of testosterone, aimed at inducing virilization. Available formulations depend on geographical region. Most commonly prescribed are parenteral testosterone cypionate, enanthate, or esters (both intramuscularly and subcutaneously) or long-acting testosterone undecanoate (8). Other options include testosterone gel or transdermal patches. If cessation of menstrual bleeding is desired, a progestational agent can be added to the treatment in case amenorrhea did not occur upon initiation of testosterone therapy (9). HT is currently continued lifelong to maintain virilization/feminization and avoid symptoms of hypogonadism. The recommended dose of different treatment modalities can be found in the Endocrine Society guideline Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline (8).

## Sex Hormones and Cardiovascular Risk

In general, CVD occurs 10 years earlier in men (10). Besides higher blood pressures and (historically) more prevalent smoking, this difference may additionally be caused by sex hormone differences, as testosterone may affect cardiovascular risk, inducing increasing lipid atherogenicity, a more unfavorable body fat distribution, increased insulin resistance, and increasing total homocysteine concentrations (11, 12). In contrast, estrogens increase thrombotic risk in women through procoagulant shifts in the hemostatic system (increased factors II, VII, VIII, X and fibrinogen levels; decreased antithrombin and protein S levels). Estrogens are also associated with development of activated protein C resistance (13).

Testosterone has androgenic and anabolic effects; stimulating protein synthesis and fat oxidation and reducing lipid storage (14). Low testosterone concentrations in cisgender men may lead to frailty, bone loss, atherosclerosis progression, coronary artery disease, diastolic cardiac dysfunction, adverse metabolic phenotype, and overall increased cardiovascular morbidity and mortality (15–21), whereas high testosterone concentrations in cisgender women with polycystic ovary syndrome (PCOS) are associated with higher cardiovascular and metabolic risk (21, 22). Visceral fat is associated with insulin resistance syndrome in both sexes; men and postmenopausal women tend to store fat predominantly in the abdominal area, premenopausal women store fat mainly in subcutaneous depots on hips and thighs (23). Visceral fat accumulation is a risk factor for CVD and type 2 diabetes mellitus (T2DM) (24). In women with increased androgen levels and postmenopausal women with decreased estradiol concentrations, visceral fat is increased compared with controls (23, 25). In men, estradiol concentrations are positively related to subcutaneous abdominal but not visceral fat owing to decreased aromatase activity in visceral compared with gluteal fat (26). Low testosterone concentrations in men are associated with visceral obesity (27).

Observational studies reported increased risk of VTE, stroke, and myocardial infarction in premenopausal women using oral contraceptives (13, 28) and higher thrombosis rates in men with prostate cancer treated with GnRH agonists, bilateral orchiectomy, or high-dose estrogens (29, 30).

Renoux et al. (31) metaanalyzed the literature on VTE risk in menopausal cisgender women prescribed hormone replacement therapy (HRT) and described a higher VTE risk associated with oral estrogen-only therapy [relative risk (RR), 1.49; 95% CI, 1.37–1.63] and oral estrogen plus progestogen therapy (RR 1.54; 95% CI, 1.44–1.65), but not with transdermal estrogen use alone or in combination with a progestogen. Observational studies and randomized controlled trials of cardiovascular risk in cisgender women taking HRT appear to have divergent results, with some studies (32, 33) reporting increased risk for CVD and myocardial infarction in postmenopausal women prescribed an estrogen–progestogen HRT combination, some studies reporting no impact of midterm (>5 years) oral estrogen plus progestogen HRT on cardiovascular mortality (34), and other studies reporting decreased risk for CVD in cisgender women given HRT (35). These differences may be related to age, time since menopause, and HRT formulation (36). Available literature on HRT and CVD was metaanalyzed in 2015 by Benkhadra et al. (37), who reported no association between HRT and cardiac or stroke mortality, independent of HRT regimen (estrogen only vs estrogen and progestogen therapy). However, as

HRT frequently consists of low-dose oral conjugated equine estrogens (CEEs) with or without medroxyprogesterone acetate, research on HRT in menopausal women may not be comparable with that in TW, who use higher doses of 17-$\beta$ estradiol combined with antiandrogens.

Plasma lipid concentrations are differently distributed in adult (not infant) men and women, with a higher HDL/LDL ratio in women. Administration of androgens to (hypogonadal) men and women results in decreased HDL concentrations, independent of estradiol concentrations (38, 39).

Arterial compliance and distensibility are necessary to convert pulsatile flow to steady perfusion flow to the organs. Arterial stiffening increases cardiac afterload and systolic blood pressure, which contributes to CVD (40). Estrogen receptors are expressed in vascular endothelial and smooth muscle cells (41, 42), and estrogen therapy has been associated with improved arterial function (43). However, both the Framingham Heart Study (44) and Collaboration for Reference Values for Arterial Stiffness (45) report no correlation between sex and carotid–femoral pulse wave velocity, the most robustly studied marker for arterial stiffening.

Previous research reported a beneficial effect of HT on surrogate cardiovascular risk markers (e.g., lipids, body composition, insulin metabolism, heart rate, blood pressure) in TW and disadvantageous effects in TM (46, 47). There have been concerns about long-term effects of HT on cardiovascular outcomes, although large prospective trials of sufficient duration have not been reported in transgender persons.

## Methods

This systematic review [in accordance with PRISMA guidelines (48)] was performed using PubMed, Scopus, and Embase, from February 15 until June 1, 2018. We searched for cardiovascular and thromboembolic risk factors, as well as events. The following cardiovascular risk factors were considered biologically modifiable and potentially affected by HT: dyslipidemia (total cholesterol, LDL, HDL, and triglycerides), insulin sensitivity (impaired fasting glucose, insulin resistance, metabolic syndrome, and T2DM), arterial blood pressure (systolic, diastolic, mean), arterial stiffness, body mass index (BMI), and waist–hip ratio (WHR). We included the following thromboembolic risk factors: serum hematocrit levels, hemoglobin levels, clotting factors, fibrinogen, (activated) partial thromboplastin time (aPTT, PTT), prothrombin time (PT), and its international normalized ratio (INR).

An overview of our search strategy can be found in the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/ vol65/issue1. Only cohort studies, cross-sectional studies, and randomized controlled trials were included. Previous review articles and metaanalyses were not included in the tables. Two investigators (JD and LVDB) independently reviewed 734 abstracts, of which 77 were retained, which contained 11 review articles. Additionally, 2 manuscripts were added between first and final submission. Only English-language articles including transgender people taking HT were considered eligible. Articles were assessed based on the GRADE tool by JD and LVDB independently.

## Results

This review includes 4 original studies on cardiovascular mortality (Table 1), 12 on cardiovascular morbidity (Table 1), 12 on blood pressure (Table 2), 25 on lipids (Supplemental Table 1), 24 on body composition (Supplemental Table 2), and 19 on markers of increased thrombosis (Supplemental Table 3).

### CARDIOVASCULAR MORTALITY

Currently, there are no long-term prospective follow-up studies available with a substantial cohort size to assess mortality risk in transgender people, only retrospective cohort studies (Table 1, Mortality section). Earlier reviews of the literature concluded that the level of evidence was too low to allow an interpretation of morbidity and mortality risk in transgender people (47, 49, 50). Several retrospective cohort studies (7, 51) reported increased mortality in TW, mainly attributable to suicides (7, 51) and not hormone-related causes. Other retrospective cohort studies (52, 53) reported no increased mortality over 4.4 years, or 10152 patient-years, of follow-up. Asscheman et al. (7) reported a higher number of cardiovascular deaths in TW than expected based on population prevalences, over 19.3 years of follow-up in a retrospective cohort study. Dhejne et al. (51) reported an adjusted hazard ratio (aHR) of 2.5 in transgender people (no substratification) compared with a Swedish control population. Asscheman et al. (7) observed an increased standardized mortality rate for ischemic heart disease [1.64 (95% CI, 1.43–1.87)] but not fatal stroke [2.11 (95% CI, 0.93–1.64)] in TW. Most cardiovascular deaths occurred in current or former smokers. Use of EE was associated with cardiovascular mortality but not with increased risk of all-cause mortality. However, we must acknowledge that the cited literature here is exclusively European.

### CARDIOVASCULAR MORBIDITY

In absence of evidence that HT according to current treatment regimens leads to increased mortality, assessing morbidity is equally important (Table 1, Morbidity section). A recent metaanalysis reported no increased risk of

**Table 1. Overview of studies on mortality and morbidity rates in transgender persons.[a]**

| Author name | Year | Study population | Type of research | Follow-up duration | Comparison condition | Number in cohort | Number in control group | Mortality | Mortality (n, %) | Mortality (n, %) control group | Effect size |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Transgender women** | | | | | | | | | | | |
| Asscheman et al. (7) | 2011 | Clinical sample | Retrospective cohort study | 19.3 ± 7.7 years | National Civil Record Registry | 966 | ? | Total | 122 (12.6%) | | SMR[b] 1.51 (1.47–1.55)[c] |
| | | | | | | | | Endocrine/diabetes | 2 (0.2%) | | SMR 0.85 (0.41–1.32) |
| | | | | | | | | Ischemic heart disease | 18 (1.8%) | | SMR 1.64 (1.43–1.87)[c] |
| | | | | | | | | CVA | 5 (0.5%) | | SMR 1.26 (0.93–1.64) |
| Van Kesteren et al. (52) | 1997 | Clinical sample | Retrospective cohort study | 10152 patient-years | National Civil Record Registry | 816 | ? | Total | 39 (4.8%) | | SMR 0.77 (0.55–1.05) |
| | | | | | | | | Myocardial infarction | 6 (0.7%) | | SMR 0.71 (0.26–1.55) |
| Asscheman et al. (53) | 1989 | Clinical sample | Retrospective cohort study | 4.4 years | Published reports on the incidence of mortality in the general population 15–64 years of age | 303 | ? | Total | 39 (12.9%) | 2.33 expected | Within the 95% CIs of the expected mortality |
| | | | | | | | | Myocardial infarction | 6 (2.0%) | 0.62 expected | Within the 95% CIs of the expected mortality |
| **Transgender men** | | | | | | | | | | | |
| Asscheman et al. (7) | 2011 | Clinical sample | Retrospective cohort study | 18.8 ± 6.3 years | National Civil Record Registry | 365 | ? | Total | 12 (3.1%) | | SMR 1.12 (0.89–1.59) |
| | | | | | | | | Endocrine/diabetes | 0 | | – |
| | | | | | | | | Ischemic heart disease | 1 (2.6%) | | SMR 1.19 (0.39–2.74) |
| | | | | | | | | CVA | 0 | | – |
| Van Kesteren et al. (52) | 1997 | Clinical sample | Retrospective cohort study | 10152 patient-years | National Civil Record Registry | 293 | | Total | 2 (0.7%) | | SMR 0.4 (0.05–1.45) |
| | | | | | | | | Myocardial infarction | 0 | | – |
| Asscheman et al. (53) | 1989 | Clinical sample | Retrospective cohort study | 3.6 years | Published reports on the incidence of mortality in the general population 15–64 years of age | 122 | | Total | 2 (1.6%) | | NA |
| | | | | | | | | Cardiovascular causes | 0 | | NA |
| **No substratification** | | | | | | | | | | | |
| Dhejne et al. (51)[d] | 2011 | Population-based sample | Retrospective cohort study | 11.4 years | Population controls matched for birth year and birth sex | 324 | 3240 | Total | 27 (8.3%) | 99 (3.1%) | aHR 2.8 (95% CI, 1.8–4.3)[c] |
| | | | | | | | | Cardiovascular mortality | 9 (2.8%) | 42 (1.9%) | aHR 2.5 (95% CI, 1.5–5.3)[c] |

**Table 1. Overview of studies on mortality and morbidity rates in transgender persons.ᵃ** *(Continued from page 122)*

| Author name | Year | Study population | Type of research | Follow-up duration | Comparison condition | Number in cohort | Number in control group | Mortality (n, %) | | Mortality (n, %) control group | Effect size | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | Compared with cisgender men (adjusted HR) | Compared with cisgender women (adjusted HR) |
| **Transgender women** | | | | | | | | | | | | |
| Getahun et al. (56) | 2018 | Clinical sample | Retrospective cohort study | 4.0 years | 10 age- and ethnicity-matched cisgender females, 10 cisgender males selected from Kaiser Permanent enrollees per transgender person | 853 | 17060 | VTE (with adjusted RR) | 61 (5.5) (95% CI, 4.3–7.0) | | 1.9 (95% CI, 1.4–2.7)ᶜ | 2.0 (95% CI, 1.4–2.8)ᶜ |
| | | | | | | | | Ischemic stroke (with adjusted RR) | 54 (4.8) (95% CI, 3.7–6.3) | | 1.2 (95% CI, 0.9–1.7) | 1.8 (95% CI, 1.1–2.9)ᶜ |
| | | | | | | | | AMI (with adjusted RR) | 33 (2.9) (95% CI, 2.1–4.1) | | 0.9 (95% CI, 0.6–1.5) | 1.8 (95% CI, 1.1–2.9)ᶜ |
| Van Kesteren et al. (52) | 1997 | Clinical sample | Retrospective cohort study | 10152 patient-years | National Civil Record Registry | 816 | ? | Arterial hypertension | 61 (7.5%) | | SIR 0.98 (0.75–1.26) | |
| | | | | | | | | VTE | 45 (5.5%) | | SIR 19.56 (12.27–26.18)ᶜ | |
| | | | | | | | | Myocardial infarction | 10 (1.2%) | | SIR 50 (0.24–0.91) | |
| | | | | | | | | CVA | 6 (0.7%) | | SIR 1.71 (0.63–3.88) | |
| | | | | | | | | Occlusion leg artery | 1 (0.1%) | | NA | |
| | | | | | | | | Angina pectoris | 4 (0.5%) | | NA | |
| Arnold et al. (62) | 2016 | Clinical sample | Retrospective cohort study | 1.9 years | – | 676 | – | VTE | 1 (0.15%) = 7.8 events/10000 person-years | – | Statistics not available | |
| Seal et al. (61) | 2012 | Clinical sample | Retrospective cohort study | 8.95–9.58 years | – | 330 | – | | | EV / EE / CEE | | |
| | | | | | | | | Thromboembolism | 4 (1.2%) | 0.6% / 0.7% / 4.49%ᶜ | $P < 0.05$ᶜ | |
| | | | | | | | | Hypertension | 9 (2.6%) | 3.7% / 1.5% / 2.2% | $P > 0.05$ | |
| | | | | | | | | Diabetes | 1 (0.3%) | 0.3% / 0.0% / 0.0% | $P > 0.05$ | |
| Nokoff et al. (55) | 2018 | Population-based | Cross-sectional study | – | General US population | 307 | (138557, 60009 Mc, 78548 Fc) | | | Mc / Fc | Mc / Fc | |
| | | | | | | | | Arterial hypertension | 29.2% (95% CI, 21.5%–36.8%) | 31.7% / 27.3% | $P > 0.01$ / $P > 0.01$ | |
| | | | | | | | | Myocardial infarction | 5.5% (95% CI, 2.5%–8.8%)ᶜ | 4.4% / 2.2%ᶜ | $P > 0.01$ / $P < 0.01$ᶜ | |
| | | | | | | | | Angina or congestive heart disease | 3.5% (95% CI, 0.8%–6.3%) | 3.9% / 2.1% | $P > 0.01$ / $P > 0.01$ | |
| | | | | | | | | Stroke | 2.6% (95% CI, 0.5%–4.7%) | 2.5% / 2.4% | $P > 0.01$ / $P > 0.01$ | |
| | | | | | | | | Diabetes | 13.4% (95% CI, 6.8%–19.9%) | 10.0% / 8.6% | $P > 0.01$ / $P > 0.01$ | |

**Table 1. Overview of studies on mortality and morbidity rates in transgender persons.[a] (Continued from page 123)**

| Author name | Year | Study population | Type of research | Follow-up duration | Comparison condition | Number in cohort | Number in control group | Mortality (n, %) | Mortality (n, %) control group | Effect size |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | **Mortality** | | |
| Asscheman et al. (53) | 1989 | Clinical sample | Retrospective cohort study | — | Published reports on the incidence of mortality and similar morbidity in the general population 15–64 years of age | 303 | ? | VTE/pulmonary embolism 19 (6.3%) | 0.42 expected | Clinically serious (statistics not available) |
| | | | | | | | | Myocardial infarction 2 (0.7%) | 0.619 expected | Statistics not available |
| | | | | | | | | TIA 1 (0.3%) | 0.54733 expected | Statistics not available |
| | | | | | | | | Arterial hypertension 14 (4.6%) | 18.708 expected | Statistics not available |
| Wierckx et al. (54) | 2013 | Clinical sample | Cross-sectional study | — | Randomly selected (3 control men and 3 control women for each participant), recruited from a population-based study in Flanders | 214 | 1259 | | Mc / Fc | Mc / Fc |
| | | | | | | | | VTE (cases/1000 persons) 60.7 | — / — | — / — |
| | | | | | | | | Myocardial infarction (cases/1000 persons) 18.7c | 12.5 / 0 | P > 0.05 / P = 0.001c |
| | | | | | | | | T2DM (cases/1000 persons) 42.0c | 6.2 / 14.9 | P = 0.04c / P = 0.021c |
| | | | | | | | | TIA/CVD 23.4 | 9.4 / 14.9 | P = 0.03c / P > 0.05 |
| Onpanna et al. (85) | 2015 | Population-based sample (Thai TW who are cabaret dancers on HT) | Cross-sectional study | — | TW not using HT | 66 | 36 | Elevated SBP (>120 mmHg) 12 (26%) | 17 (41%) | $\chi^2 = 0.13$ |
| | | | | | | | | Elevated DBP (>80 mmHg) 0 | 0 | — |
| | | | | | | | | Elevated TC (>200 mg/dL) 19 (37%) | 16 (37%) | $\chi^2 = 0.95$ |
| | | | | | | | | Elevated TG (>150 mg/dL) 4 (8%) | 8 (19%) | $\chi^2 = 0.11$ |
| | | | | | | | | Elevated LDL (>100 mg/dL) 32 (63%) | 28 (65%) | $\chi^2 = 0.81$ |
| | | | | | | | | Low HDL (<40 mg/dL) 3 (6%) | 7 (16%) | $\chi^2 = 0.10$ |
| Wierckx et al. (58) | 2012 | Clinical sample | Cross-sectional study | — | TM | 50 | 50 | All cardiovascular events 6 | 0 | Statistics not available |
| | | | | | | | | DVT 1 | 0 | Statistics not available |
| | | | | | | | | Cerebral thrombosis 2 | 0 | Statistics not available |
| | | | | | | | | PAD 1 | 0 | Statistics not available |
| | | | | | | | | Venous ulcer 1 | 0 | Statistics not available |
| | | | | | | | | Myocardial infarction 1 | 0 | Statistics not available |

**Table 1. Overview of studies on mortality and morbidity rates in transgender persons.ᵃ (Continued from page 124)**

| Author name | Year | Study population | Type of research | Follow-up duration | Comparison condition | Number in cohort | Number in control group | Mortality | Mortality (n, %) | Mortality (n, %) control group | | Effect size |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Fc | Mc | |
| Schlatterer et al. (103) | 1998 | Clinical sample | Cross-sectional study | – | TM | 46 | 42 | Thrombosis | 0 | 0 | | – |
| De Cuypere et al. (57) | 2005 | Clinical sample 1 year after gender-affirming surgery | Cross-sectional study | – | TM 1 year after gender-affirming surgery | 32 | 23 | Stroke | 1 (1.3%) | 0 | | Statistics not available |
| **Transgender men** | | | | | | | | | | | | |
| Van Kesteren et al. (52) | 1997 | Clinical sample | Retrospective cohort study | 10152 patient-years | National Civil Record Registry | 293 | ? | Arterial hypertension | 12 | | | SIR 0.84 (0.43-1.47) |
| | | | | | | | | VTE | 1 | | | SIR 9.09 (0.23-50.65) |
| | | | | | | | | Myocardial infarction | 1 | | | SIR 0.34 (0.01-1.92) |
| | | | | | | | | Angina pectoris | 1 | | | NA |
| Nokoff et al. (55) | 2018 | Population-based | Cross-sectional study | – | General US population | 197 | (138557, 60009 Mc, 78548 Fc) | Arterial hypertension | 25.2% (95% CI, 12.7%–37.8%) | 27.3% | 31.7% | P > 0.01 |
| | | | | | | | | Myocardial infarction | 25.2% (95% CI, 0.0%–4.3%) | 27.3% | 31.7% | P > 0.01 |
| | | | | | | | | Angina or congestive heart disease | 3.1% (95% CI, 0.4%–5.8%) | 2.1% | 3.9% | P > 0.01 |
| | | | | | | | | Stroke | 2.3% (95% CI, 0.2%–4.3%) | 2.5% | 2.4% | P > 0.01 |
| | | | | | | | | Diabetes | 4.4% (95% CI, 1.5%–7.4%) | 8.6% | 10.0% | P > 0.01 |
| Asscheman et al. (53) | 1989 | Clinical sample | Retrospective cohort study | 3.6 years | Published reports on the incidence of mortality and similar morbidity in the general population 15–64 years of age | 122 | ? | VTE | 0 | – | | NA |
| | | | | | | | | Myocardial infarction | 0 | – | | NA |
| | | | | | | | | Arterial hypertension | 3 (2.4%) | 1.274 expected | | Statistics not available |
| Wiercx et al. (54) | 2013 | Clinical sample | Cross-sectional study | – | Randomly selected (3 control men and 3 control women for each participant), recruited from a population-based study in Flanders | 138 | 828 | VTE (cases/1000 persons) | 14.5 | – | – | – |
| | | | | | | | | Myocardial infarction (cases/1000 persons) | 0 | 0 | 7.3 | P > 0.05 |
| | | | | | | | | T2DM (cases/1000 persons) | 36.2ᶜ | 0 | 7.3 | P < 0.001ᶜ |

**Table 1. Overview of studies on mortality and morbidity rates in transgender persons.[a]** *(Continued from page 125)*

| Author name | Year | Study population | Type of research | Follow-up duration | Comparison condition | Number in cohort | Number in control group | Mortality (n, %) | | Mortality (n, %) control group | | Effect size |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Wierckx et al. (58) | 2012 | Clinical sample | Cross-sectional study | – | TW | 50 | 50 | All cardiovascular events | 0 | 6 | | Statistics not available |
| | | | | | | | | DVT | 0 | 1 | | Statistics not available |
| | | | | | | | | Cerebral thrombosis | 0 | 2 | | Statistics not available |
| | | | | | | | | PAD | 0 | 1 | | Statistics not available |
| | | | | | | | | Venous ulcer | 0 | 1 | | Statistics not available |
| | | | | | | | | Myocardial infarction | 0 | 1 | | Statistics not available |
| Schlatterer et al. (103) | 1998 | Clinical sample | Cross-sectional study | – | TW | 88 (46 TW, 42 TM) | – | Thrombosis | 0 | 0 | | – |
| De Cuypere et al. (57) | 2005 | Clinical sample 1 year after gender-affirming surgery | Cross-sectional study | – | TW 1 year after gender-affirming surgery | 23 | 32 | Stroke | 1 (4.3%) | 1 (3.1%) | | Statistics not available |
| | | | | | | | | T2DM | 1 (4.3%) | ? | | Statistics not available |
| | | | | | | | | Hyperlipidemia | 7.1% (n, not shown) | ? | | Statistics not available |
| | | | | | | | | Arterial hypertension | 32% (n, not shown) | ? | | Statistics not available |

**Gender-nonconforming people**

| Author name | Year | Study population | Type of research | Follow-up duration | Comparison condition | Number in cohort | Number in control group | | GNC-F | GNC-M | Fc | Mc | Effect size |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nokoff et al. (55) | 2018 | Population-based | Cross-sectional study | – | General US population | 197 | (138557, 60009 Mc, 78548 Fc) | Arterial hypertension | 37.0% (95% CI, 15.9%–58.2%) | 23.0% (95% CI, 7.9%–38.1%) | 27.3% | 31.7% P > 0.01 | |
| | | | | | | | | Myocardial infarction | 2.1% (95% CI, 0.0%–22.0%) | 8.7% (95% CI, 0.0%–4.3%) | 27.3% | 31.7% P > 0.01 | |
| | | | | | | | | Angina or congestive heart disease | 1.3% (95% CI, 0.0%–2.8%) | 3.4% (95% CI, 0.0%–6.7%) | 2.1% | 3.9% P > 0.01 | |
| | | | | | | | | Diabetes | 12.7% (95% CI, 0.0%–26.9%) | 3.2% (95% CI, 0.0%–6.6%) | 8.6% | 10.0% P > 0.01 | |

**No substratification**

| Author name | Year | Study population | Type of research | Follow-up duration | Comparison condition | Number in cohort | Number in control group | Mortality (n, %) | | Mortality (n, %) control group | | Effect size |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ott et al. (124) | 2008 | Clinical sample | Retrospective cohort study | | | 162 | – | VTE | 0 | – | | NA |

[a] The table has been subdivided by gender identity (TW, TM, no stratification), by decreasing sample number.

[b] SMR, standardized mortality ratio; CVA, cerebrovascular accident; NA, not applicable; Mc, male controls; Fc, female controls; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; PAD, peripheral arterial disease; GNC-F, birth-assigned female gender-nonconforming people; GNC-M, birth assigned male gender nonconforming people.

[c] Statistically significant results.

[d] Dhejne et al. also calculated aHRs for TM and TW separately; total mortality: TW, 2.4 (1.4–4.1) and TM, 3.8 (1.8–7.9); cardiovascular mortality not applicable.

**Table 2. Overview of studies on blood pressure (in mmHg) in transgender persons.[a]**

| Author name | Year | Study population | Type of research | Follow-up duration | Comparison condition | Number in cohort | Number in control group | Mean value outcome in intervention + SD | Mean value outcome control/baseline + SD | Statistics (P value) | Type of gender-affirming HT |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Transgender women** | | | | | | | | | | | |
| Onpanna et al. (85) | 2015 | Population-based sample (Thai TW who are cabaret dancers on HT) | Cross-sectional study | – | TW not using HT | 66 | 36 | SBP[b] 114.8 ± 15.4<br>DBP 72.9 ± 11.3 | 117.8 ± 11.8<br>75.6 ± 9.8 | P > 0.05<br>P > 0.05 | Self-administration dose and schedule; commercially available contraceptive pills and injectables; dosages varied arbitrarily |
| Wierckx et al. (58) | 2012 | Clinical sample after gender-affirming surgery | Cross-sectional study | – | TM | 50 | 50 | SBP 124.7 ± 14.4<br>DBP 81.3 ± 10.7<br>MABP 95.8 ± 10.1 | 124.8 ± 16.6<br>77.1 ± 10.1<br>93.0 ± 11.2 | P = 0.208<br>P = 0.002[c]<br>P = 0.008[c] | TW: estrogens (unspecified) TM: testosterone (unspecified) |
| Jarin et al. (71) | 2017 | Adolescent clinical sample | Retrospective cohort study | 6 years | Baseline values | 44 | 44 | SBP 125<br>DBP 72 | 121<br>72 | P > 0.05<br>P > 0.05 | Estrogen (unspecified): oral 1, 2, 3, 4, 6, or 8 mg daily; IM 20, 40, or 80 mg monthly; transdermally 0.025, 0.05, 0.100, or 0.200 mg weekly |
| Prior et al. (125) | 1989 | Clinical sample: TW treated with estrogens plus spironolactone | Controlled clinical trial | 1 year | TW treated with high-dose estradiol | 23 | 27 | SBP 127.8 ± 13.6<br>DBP 79.8 ± 10.4 | 129.3 ± 17.3<br>77.7 ± 10.1 | P > 0.05<br>P > 0.05 | Intervention: CEE 0.625 mg/day, increasing to 2.5 mg twice/day for 3 of 4 weeks + spironolactone 100 to 200 mg/day, increased to achieve T reduction Control: CEE alone |
| Olson-Kennedy et al. (64) | 2017 | Adolescent clinical sample | Prospective cohort study | 2 years | Baseline values | 23 | 23 | SBP 124.84 ± 12.10<br>DBP 70.80 ± 7.68 | 122.68 ± 14.4<br>71.08 ± 10.66 | P = 0.465<br>P = 0.898 | Spironolactone (100-200 mg orally per day) or a GnRH analog + 17β estradiol (oral 1-6 mg each day, injectable 20-30 mg IM every 14 days), in some cases + progesterone |
| Vita et al. (65) | 2018 | Clinical sample | Retrospective cohort study | 30 ± 25.9 months | – | 21 | 21 | SBP 112.9 ± 5.8<br>DBP 70.0 ± 7.2 | 113.3 ± 8.2<br>71.7 ± 7.5 | P < 0.05[c]<br>P > 0.05 | EE (n = 4) or EV (n = 17) + CPA 50-100 mg |
| Elbers et al. (75) | 2003 | Clinical sample | Prospective cohort study | 12 months | Baseline values | 20 | 20 | SBP 134.1 ± 12.9<br>DBP 75.8 ± 9.9 | 126.9 ± 10.2<br>70.1 ± 8.5 | P = 0.01[c]<br>P < 0.01[c] | EE 100 µg/day + CPA 100 mg/day |
| Deutsch et al. (82) | 2015 | Clinical sample | Prospective cohort study | 6 months | Baseline values | 16 | 23 | SBP 120 ± 15.5<br>DBP 67 ± 12 | 130.5 ± 11.5<br>78 ± 21 | P = 0.006[c]<br>P = 0.001[c] | 17β estradiol 2 mg twice daily (n = 14), 100 µg estradiol patch (n = 1) EV 20 mg IM/2 weeks (n = 1) + spironolactone 50 mg twice daily (n = 20); 10 had doses increased to 100 mg twice daily at the 3-month mark |

**Table 2. Overview of studies on blood pressure (in mmHg) in transgender persons.[a] (Continued from page 127)**

| Author name | Year | Study population | Type of research | Follow-up duration | Comparison condition | Number in cohort | Number in control group | Measure | Mean value outcome in intervention + SD | Mean value outcome control/baseline + SD | Statistics (P value) | Type of gender-affirming HT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Fernandez et al. (66) | 2017 | Adolescent clinical sample | Retrospective cohort study | 6-18 months | Baseline values | 15 | 15 | SBP | 131 ± 3 | 27.7 ± 1.9 | P > 0.05 | 50% oral estrogen (unspecified) average daily dose 1.44 mg/day (visit 1) to 1.71 mg/day (visit 2), 50% transdermal estrogen (22% at visit 1; 14% at visit 2) or IM estrogen (22% at visit 1; 36% at visit 2) |
| | | | | | | | | DBP | 82 ± 2 | 125 ± 4 | P > 0.05 | |
| **Transgender men** | | | | | | | | | | | | |
| Jarin et al. (71) | 2017 | Adolescent clinical sample | Retrospective cohort study | 6 years | Baseline values | 72 | 72 | SBP | 118 | 118 | P > 0.05 | Testosterone (unspecified) start with 25 mg/week SC, increased to 25, 50, or 100 mg/week |
| | | | | | | | | DBP | 71 | 69 | P > 0.05 | |
| Wierckx et al. (58) | 2012 | Clinical sample gender-affirming surgery | Cross-sectional study | – | TW | 50 | 50 | SBP | 124.8 ± 16.6 | 124.7 ± 14.4 | 0.208 | TW: estrogens (unspecified) TM: testosterone (unspecified) |
| | | | | | | | | DBP | 77.1 ± 10.1 | 81.3 ± 10.7 | 0.002[c] | |
| | | | | | | | | MABP | 93.0 ± 11.2 | 95.8 ± 10.1 | 0.008[c] | |
| Emi et al. (63) | 2007 | Clinical sample on testosterone therapy | Cross-sectional study | – | TM not receiving testosterone | 48 | 63 | SBP | 117.4 ± 10.2 | 110.4 ± 9.4 | P < 0.01[c] | TES IM biweekly 150 or 250 mg |
| | | | | | | | | DBP | 68.6 ± 8.4 | 64.6 ± 6.9 | P < 0.02[c] | |
| | | | | | | | | MABP | 86.6 ± 9.0 | 81.1 ± 7.6 | P < 0.01[c] | |
| Mueller et al. (77) | 2007 | Clinical sample | Prospective cohort study | 12 months | Baseline values | 35 | 35 | SBP | 133.71 ± 11.33 | 129.43 ± 13.38 | P = 0.04[c] | TU every 12 weeks |
| | | | | | | | | DBP | 84.00 ± 5.25 | 81.14 ± 8.14 | P = 0.02[c] | |
| Olson-Kennedy et al. (64) | 2017 | Adolescent clinical sample | Prospective cohort study | 2 years | Baseline values | 35 | 35 | SBP | 128.03 ± 11.40 | 115.62 ± 15.15 | P < 0.001[c] | TC SC 12.5–75 mg weekly |
| | | | | | | | | DBP | 72.32 ± 12.15 | 67.15 ± 12.57 | P = 0.024[c] | |
| Deutsch et al. (82) | 2015 | Clinical sample | Prospective cohort study | 6 months | Baseline values | 31 | 34 | SBP | 123 ± 14 | 120 ± 23 | P > 0.05 | TC SC starting at 50 mg/wk; 10 subjects increased to 70 mg/wk after 3 mol/L, TG (n = 2) Testosterone transdermal patch 4 mg/day (n = 1) |
| | | | | | | | | DBP | 70 ± 16 | 72 ± 16 | P > 0.05 | |
| Elbers et al. (75) | 2003 | Clinical sample | Prospective cohort study | 12 months | Baseline values | 17 | 17 | SBP | 122.4 ± 8.2 | 121.4 ± 9.9 | P > 0.05 | TE 250 mg IM every 2 weeks |
| | | | | | | | | DBP | 66.9 ± 4.9 | 67.1 ± 7.5 | P > 0.05 | |
| Chandra et al. (80) | 2010 | Clinical sample | Prospective cohort study | 12 months | Baseline values | 12 | 12 | MABP | 91 ± 16 | 87 ± 14 | P = 0.16 | 50-125 mg of TES, TC or TE every 2 weeks |
| Fernandez et al. (66) | 2017 | Adolescent clinical sample | Retrospective cohort study | 6-18 months | Baseline values | 10 | 10 | SBP | 124 ± 4 | 122 ± 5 | P > 0.05 | Testosterone IM average daily dose 11 mg |
| | | | | | | | | DBP | 76 ± 2 | 75 ± 4 | P > 0.05 | |
| Vita et al. (65) | 2018 | Clinical sample | Prospective cohort study | 12 months | Baseline values | 11 | 11 | SBP | 113.3 ± 8.2 | 107.1 ± 4.9 | P > 0.05 | TE (n = 10) or TU (n = 1) |
| | | | | | | | | DBP | 71.7 ± 7.5 | 68.6 ± 3.8 | P > 0.05 | |

[a] The table has been subdivided by gender identity (TW, TM), by decreasing sample number.
[b] SBP, systolic blood pressure; DBP, diastolic blood pressure; MABP, mean arterial blood pressure; IM, intramuscular; T, testosterone; CPA, cyproterone acetate; SC, subcutaneous; TES, testosterone esters; TU, testosterone undecanoate; TC, testosterone cypionate; TE, testosterone enthanate.
[c] Statistically significant results.

myocardial infarction, stroke, or VTE in transgender people, probably because of lack of reported outcomes from eligible studies *(47)*. Two cross-sectional studies *(54, 55)* reported increased prevalence of myocardial infarction in TW taking HT compared with an age-matched group of cisgender women but not compared with cisgender men.

Three large retrospective cohort studies *(51, 54, 56)* reported increased myocardial infarction and cerebrovascular disease rates in TW prescribed HT compared with cisgender people. However, only the study by Wierckx et al. *(54)* provided elaborate information on type of gender-affirming HT (which included EE). Getahun et al. *(56)* reported an increased incidence of acute myocardial infarction in TW compared with cisgender women but not compared with cisgender men. A population-based survey in the US reported higher myocardial infarction odds in TW compared with cisgender women but not compared with cisgender men. The risk for cardiovascular events was comparable with the general population for TM and gender-nonconforming people. However, they did not specify how many transgender people were taking HT *(55)*. Another large retrospective cohort *(52)* reported a possible reduction in myocardial infarction-related morbidity in TW compared with cisgender men.

### STROKE

Stroke and/or transient ischemic attack (TIA) have been described in TW *(53, 57, 58)*, although studies that computed RRs or aHRs are scarce *(52, 54–56)*. The cross-sectional study by Wierckx et al. *(54)* showed a higher prevalence of TIA/CVD in TW (23.4 cases/1000 persons) compared with cisgender men (9.4 cases/1000 persons) but not compared with cisgender women. A more recent study by Getahun et al. *(56)* reported an increased incidence of stroke in TW compared with cisgender women [aHR, 1.8 (95% CI, 1.1–2.9)] but not compared with cisgender men [aHR, 1.2 (95% CI, 0.9–1.7)]. However, Getahun et al. *(56)* did not provide detailed information on type of estrogen used by the TW in their study. These results are contradicted by 2 older large retrospective cohort studies *(52, 53)* and 1 recent (2018) cross-sectional study. Asscheman et al. *(53)* reported no increased risk for TIA in TW (statistics not available). Van Kesteren et al. *(52)* reported a standardized incidence ratio (SIR) of 1.71 (95% CI, 0.63–3.88) in TW compared with the National Civil Record Registry. The population-based cross-sectional study by Nokoff et al. *(55)* reported no increased stroke incidence compared with control cisgender men and women.

Getahun et al. *(56)* reported a higher aHR for stroke in TM [2.1 (95% CI, 1.3–3.5)] compared with cisgender men [1.1 (95% CI, 0.6–2.0)] and cisgender women [1.3 (95% CI, 0.7–2.5)]. On the other hand, Nokoff et al.

*(55)* showed no increased stroke incidence in TM compared with control cisgender men and women. Maraka et al. *(47)* recently metaanalyzed the literature on cardiovascular risk. Of the 340 individuals taking testosterone therapy included in the metaanalysis, no cases of stroke were reported.

### ARTERIAL HYPERTENSION

One review article *(50)* reported sodium and water retention in 1.7% of TM (resolved after testosterone dose reduction). Increased blood pressure was documented in 4.1%, comparable with prevalence studies in healthy population-based samples *(22)*. A large retrospective study *(52)* observed only 3 cases of hypertension in TM and 14 in TW, with an SIR of 0.34 for TW (not calculated in TM), indicating no increased risk for hypertension.

### VTE

Given the prothrombotic actions of estrogens, increased thrombosis risk is theoretically expected in TW *(59)*. However, increased VTE risk is predominantly documented in older studies reporting on TW prescribed EE. Results on VTE risk in TW were previously reviewed by Shatzel et al. *(60)*, who reported a higher rate of VTE with certain estrogens. The rate is highest with oral estrogen therapy, particularly EE, and lowest with transdermal estrogen and EV. Most cases of thrombosis occurred in the first year after starting estrogen therapy and in TW who smoked. One older retrospective study *(52)* reported a 20-fold increase in VTE complications in TW compared with cisgender women. Wierckx et al. *(58)* reported VTE in 1 TW (n = 1, 2.0%), whereas none of the (non–age-matched) TM (0%) experienced deep venous thrombosis (DVT). Seal et al. *(61)* reported increased VTE risk in TW taking oral CEEs (4.4%) compared with TW prescribed oral EV or EE (<1.0%). In a large retrospective cohort study *(52)*, all but 1 TW who experienced VTE were prescribed EE, and most adverse events occurred within the first year of HT. VTE risk did not increase with age. Getahun et al. *(56)* reported a 5.5 adjusted RR for VTE compared with cisgender peers. However, information on type of oral estradiol was not published. A recent study *(62)* reported VTE in 1 TW after 2 years of taking estradiol (4 mg/day) and spironolactone (200 mg/day), resulting in 0.15% VTE rate with mean follow-up duration of 1.9 years.

### T2DM

Although Nokoff et al. *(55)* reported no increased odds for diabetes in transgender compared with cisgender adults, Wierckx et al. *(54)* reported a higher prevalence of T2DM compared with cisgender controls, with almost all diagnoses made before starting HT in TW. However, results may be biased by endocrine screening before initiating HT.

# Reviews

**MARKERS OF CARDIOVASCULAR AND METABOLIC MORBIDITY**
Markers of cardiovascular and metabolic morbidity were grouped in longer term (e.g., altered blood pressure, lipids, increased insulin resistance) and short-term changes (thrombosis).

*Arterial blood pressure.* The available research on the impact of HT on systolic/arterial blood pressure showed conflicting results in cross-sectional and prospective studies (Table 2).

Two cross-sectional studies report conflicting results (58, 63); Wierckx et al. (58) reported higher mean arterial and diastolic (but not systolic) blood pressure in non–age-matched TW taking HT compared with TM prescribed HT, whereas Emi et al. (63) reported higher systolic, mean arterial, and diastolic blood pressure in TM given HT compared with TM not taking HT.

In prospective studies of transgender adults (64–66), mean arterial, systolic, and diastolic blood pressure increased or remained stable in TM, whereas it decreased or remained stable in TW. This could not be explained by studies on arterial stiffness (63, 67–69).

*Lipids.* Results regarding the impact of testosterone therapy on lipid levels are often conflicting (Supplemental Table 1). Most available studies report an increase in HDL concentrations and a decrease in LDL in TW, and a decrease in HDL concentrations in TM (64, 66, 69–82). The impact of HT on LDL in TM is inconclusive (65, 66, 78, 81, 83). Multiple studies report no change in triglyceride concentrations in transgender people (63–66, 70–75, 77, 79–81, 83–87).

However, the mechanism behind the observed changes in plasma lipid levels after administration of HT remains unknown, and it is unsure whether this will affect cardiovascular risk, as several large cardiovascular outcome trials concluded that HDL-altering treatment did not affect cardiovascular outcome (88, 89). It appears that HDL metabolism rather than circulating HDL concentrations determines atherogenicity (38). Studies in transgender people are again inconclusive (70, 75). Given the small numbers of studies assessing lipid metabolism in transgender people, we cannot unequivocally link HT to atherosclerotic risk. Prospective studies with sufficient sample size, adhering to currently advised treatment regimens and assessing both lipid concentrations and metabolism, are necessary to assess atherosclerotic risk.

*Markers of insulin resistance.* Insulin resistance has been described in cisgender men with hypogonadism (90) and in cisgender women with PCOS (91); thus, one would expect increased insulin resistance in TM receiving testosterone and in TW receiving testosterone blockers. The current literature covering transgender people provides no uniform evidence of increased insulin resistance in transgender people taking HT (57, 63, 64, 71, 72, 79–81) (Supplemental Table 2), although other markers of insulin sensitivity decreased during the first months of testosterone therapy in TM compared with baseline (87) or compared with cisgender male reference ranges (92). These results are contradicted in the randomized controlled trial by Pelusi et al. (73), in which higher fasting glucose concentrations were reported in TM after 12 months of HT, independent of type of testosterone. It remains to be determined whether this will result in insulin resistance. However, supraphysiological doses of testosterone may induce insulin resistance in TM and cisgender women (75, 93). Five prospective studies (64, 72, 74, 75, 81) observed no change in fasting glucose concentrations in TW, whereas 2 studies (74, 75) observed an increase in insulin resistance markers. However, the available prospective studies on insulin resistance and metabolic risk in transgender people mainly report on short-term data, and it remains unsure whether the administration of testosterone may have effects on insulin sensitivity, as this has not been described in longer term studies.

*Body composition.* In general, most of the studies describe a status quo or increase in BMI in transgender people (66, 72, 75–77, 80–82, 94–97), although transgender people taking HT are not more likely to be obese compared with cisgender age-matched controls (54, 63, 94) (Supplemental Table 2). WHR tends to change toward the desired gender (81, 98), which is also reflected in a decrease in subcutaneous fat area and an increase in visceral fat in TM (75, 76, 98, 99) and an increase in subcutaneous fat in TW (75, 76, 98) after initiation of HT. However, an increase in visceral fat has been described in TW (75, 98), probably because of decreased aromatase activity in visceral fat in birth-assigned males compared with birth-assigned females (26). Visceral fat is a strong correlate of metabolic risk factors (100). It remains to be determined whether the increase in visceral fat in transgender people will result in higher cardiometabolic morbidity in the longer term.

*Markers of increased thrombotic risk.* Several studies describe an increase in hemoglobin and hematocrit levels in TM during the first year of HT, with the most pronounced increase during the first 3 months (11, 12, 20, 63–66, 71, 73, 74, 78, 83, 101–103) (Supplemental Table 3). Hematocrit levels remain stable after the first year of HT (11, 12, 83, 101, 102). Although testosterone therapy may induce erythrocytosis, clinically significant erythrocytosis is rare (78, 81, 83, 101, 102). In addition, testosterone therapy is also associated with an increase in hemoglobin and hematocrit levels toward cisgender male reference ranges, with no clinically significant erythrocytosis and no increased risk for VTE (11, 12, 20, 63–66, 71, 73, 74, 78, 81, 83, 101–103).

Several studies attempted to unravel the effects of sex steroids on the coagulation pathway (Supplemental Table 3). HT does alter elements of the coagulation pathway, which may theoretically lead to increased thrombosis risk in TM *(86, 104–106)* and TW *(86)*, as well as decreased thrombosis risk in TM *(107)* and TW *(105)*. The observed changes did not result in changes in coagulation parameters (PT, aPTT, thrombin time, and fibrinogen concentration) in TM *(77)* and TW *(86)* 6 to 12 months after the initiation of HT. These studies are limited by small cohort sizes.

## Discussion

Given the relatively short follow-up duration in studies assessing cardiovascular mortality and morbidity and older studies reporting on TW using EE, it is possible that effects of HT on cardiovascular mortality/morbidity (if any) will become apparent only after long-term HT. Assessing markers of CVD may give an idea about cardiovascular, metabolic, and thromboembolic risk in transgender people prescribed HT. However, the available literature remains inconclusive on this topic. It is also possible that differences in type of gender-affirming HT are (partially) responsible for conflicting results among different studies. To date, there are no randomized controlled clinical trials available reporting on cardiovascular mortality, morbidity, and/or risk among different HT formulations/doses.

The available literature does not suggest increased risk for arterial hypertension, dyslipidemia, or insulin resistance in TM, despite some markers of cardiovascular and metabolic disease suggesting increased cardiometabolic risk in TM (increasing WHR, increasing percentage of visceral fat, increasing/stable blood pressure and BMI, and inconclusive effects on LDL) and in TW (increasing percentage of visceral fat, increasing/stable BMI). In contrast, other markers suggest a decreased risk in TW (stable insulin resistance, decreasing/stable blood pressure, and decreasing LDL and WHR). However, absence of proof is not proof of absence; in this regard, the importance of ongoing large-scale prospective studies/registries and of optimal management of conventional risk factors (e.g., weight, LDL cholesterol, blood pressure, smoking) as applicable to all cannot be overemphasized. Some conflicting results can be explained by the older mean age of TW compared with TM, geographical location, HT regimen, minority stress, or lifestyle factors. Transgender people are more likely to smoke *(108)*, consume more alcohol *(109)*, and have a lower level of physical activity *(110)* compared with cisgender population references, and Vilas et al. *(111)* observed a mean daily nutrient intake of 3614.3 ± 1314 kcal. In addition, transgender people often report feelings of discrimination resulting from transgender status (minority stress) *(112–114)*, which may be associated with increased stress, health risk behavior, and long-term poor health outcomes *(115)*.

Based on available evidence, no increased risk for cardiovascular mortality and morbidity is seen, when adhering to recent treatment regimens. However, the available literature is currently inadequately powered to detect this lack of difference. We must acknowledge the fact that our data are limited by a relatively short follow-up duration, without data on older transgender people *(46, 47, 52)*. More, large prospective cohort studies such as the ongoing STRONG *(116)*, ENIGI *(117)*, and GETS *(118)* studies are needed, which should include people of different age categories and take confounding factors (e.g., lipid levels/metabolism, physical activity, body composition, dietary intake, mental well-being) into account. Also, addition of the sociodemographic marker "gender identity" to national health registries may help assess the risk for cardiovascular and metabolic morbidities in transgender people and may contribute to research on gender nonbinary people, who are frequently ignored in the available literature. This will result in large databases, enabling faster detection of subtle changes in cardiometabolic risk factors, morbidity, and/or mortality. However, we must also keep in mind that there is sustainable evidence that HT decreases or even resolves feelings of gender dysphoria in transgender persons and ameliorates quality of life *(96, 119–122)*, whereas the available literature on cardiovascular mortality and morbidity in transgender people is limited in its level of evidence.

The Endocrine Society guideline *(8)* suggests monitoring weight, blood pressure, and lipids at regular intervals. Without clear evidence of increased risk, absolute cardiovascular risk calculation should be performed according to local guidelines for the general population before the initiation of gender-affirming hormones and during follow-up. In addition, because emotional stress can be as detrimental to cardiovascular health as physical stress *(123)*, we recommend addressing psychological well-being and, if necessary, referral to a mental health professional. As it is unclear which reference intervals are more relevant for transgender individuals, risk calculation using calculator settings for birth-assigned males (for safety measures, these are more cautious compared with settings for birth-assigned females) provides a sensitive estimate of risk for TM and TW, but may lack specificity. If cardiovascular risk factors emerge, they should be managed according to established population-based guidelines.

In conclusion, although the currently available literature lacks power and is at moderate risk for bias, most of the studies reported no increase in cardiovascular morbidity for transgender people taking HT in short to medium (10 years) follow-up periods. Known biochemical markers of CVD show conflicting results for transgender people prescribed HT. The degree to which CVD is at-

tributable to traditional risk factors rather than sex steroids themselves remains uncertain.

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