

## RESEARCH LETTER

# Occurrence of Acute Cardiovascular Events in Transgender Individuals Receiving Hormone Therapy

## Results From a Large Cohort Study

In hypogonadal/postmenopausal individuals, hormone therapy has been associated with an increased risk for cardiovascular events (CVEs). A steeply growing population that often receives exogenous hormones is transgender individuals. Although transgender individuals hypothetically have an increased risk of CVEs, there is little known about the occurrence of CVEs in this population.<sup>1</sup> Therefore, we determined the incidences of acute/spontaneous strokes (ischemic/hemorrhagic, transient ischemic attack, or subarachnoid hemorrhage), myocardial infarctions (MIs), and venous thromboembolic events (VTEs) in transwomen and transmen receiving transgender hormone therapy (THT). Subsequently, we compared these incidences with those reported in women and men from the general population.

This study was approved by our local ethical committee, with a waiver for informed consent.

We reviewed the medical records of all 6793 individuals who visited our gender clinic between 1972 and 2015. However, we only included individuals who received THT prescribed by our center or an affiliate, whose date of start of THT was known, and who had at least 1 follow-up visit. We excluded participants who had discontinued THT for an extended period or who had used female and male sex hormones alternately. Of the remaining 3927 participants, the records were screened by physicians and medical students for letters/notes from physicians indicating clearly that an acute CVE had occurred. We excluded subjects who had experienced a CVE before starting THT ( $n=52$ ). The final population consisted of 2517 transwomen (median age 30 years) and 1358 transmen (median age 23 years). From those who experienced multiple CVEs during THT ( $n=3$ ), only the first event was taken into account. THT consisted of estrogens ( $\pm$ antiandrogens) in transwomen and testosterone in transmen. Adolescents usually received puberty suppressors, with the addition of THT from the age of 16 years. Statistical analyses were performed using OpenEpi version 3.01 (<http://www.openepi.com>) and Stata version 15.1 (<https://www.stata.com>). (Age-adjusted) standardized incidence ratios (SIRs) with 95% CIs were calculated using multiple steps. First, we determined the number of CVEs that occurred during THT (observed cases). Second, for each separate CVE, we created age groups comparable to those used by reference studies examining the occurrence of CVEs in the general Dutch or Norwegian populations,<sup>2–4</sup> and determined the follow-up duration (person-years) per age group. Third, we calculated overall expected cases, based on reported age- and sex-specific incidence rates by the reference studies,<sup>2–4</sup> and our age group-specific follow-up durations. Finally, Mid- $P$  exact tests were performed.

For transwomen, the total follow-up duration was 22830 years. The mean and median follow-up durations were 9.07 (SD, 8.72) and 5.95 years (range, 0.01–54.77), respectively. For transmen, the total follow-up duration was 11003 years. The mean and median follow-up durations were 8.10 years (SD, 8.82) and 4.10 years (range,

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**Table.** Standardized Incidence Ratios for Acute Cardiovascular Events in Transwomen and Transmen Receiving Hormone Therapy

| Acute Cardiovascular Events | OCs (IR)* | Using Women as Reference |                   | Using Men as Reference |                   |
|-----------------------------|-----------|--------------------------|-------------------|------------------------|-------------------|
|                             |           | ECs                      | SIR (95% CI)      | ECs                    | SIR (95% CI)      |
| Transwomen                  |           |                          |                   |                        |                   |
| Stroke                      | 29 (127)  | 12.01                    | 2.42 (1.65–3.42)† | 16.08                  | 1.80 (1.23–2.56)† |
| Myocardial infarction       | 30 (131)  | 11.38                    | 2.64 (1.81–3.72)† | 38.03                  | 0.79 (0.54–1.11)  |
| Venous thromboembolism      | 73 (320)  | 13.22                    | 5.52 (4.36–6.90)† | 16.04                  | 4.55 (3.59–5.69)† |
| Transmen                    |           |                          |                   |                        |                   |
| Stroke                      | 6 (55)    | 3.49                     | 1.72 (0.70–3.58)  | 4.10                   | 1.46 (0.59–3.04)  |
| Myocardial infarction       | 11 (100)  | 2.98                     | 3.69 (1.94–6.42)† | 10.99                  | 1.00 (0.53–1.74)  |
| Venous thromboembolism      | 2 (18)    | 4.84                     | 0.41 (0.07–1.37)  | 5.56                   | 0.36 (0.06–1.19)  |

ECs indicates expected cases; IR, incidence rate; OCs, observed cases; and SIR, standardized incidence ratio.

\*Per 100 000 person-years.

†Significant finding.

0.02–41.66), respectively. The SIRs in the Table indicate that transwomen had a higher adjusted incidence of strokes and VTEs than reference women and men, and that both transwomen and transmen had a higher risk of MIs than reference women. Because ethinylestradiol could be responsible for the increased cardiovascular risk in transwomen, we performed subanalyses in which we excluded transwomen who started THT before 2001 (after 2001, ethinylestradiol was replaced by more natural estrogens). However, only for VTEs the SIRs of this subpopulation were more favorable than the SIRs of the total population (3.92 versus 5.52 when using women as reference, and 3.39 versus 4.55 when using men as reference).

It is interesting to note that our results regarding transwomen are in line with recent literature. Getahun et al<sup>5</sup> also found higher rates of strokes and VTEs in transwomen relative to reference women and men, and of MIs relative to reference women. However, they could not draw conclusions about an increased risk for CVEs in transmen during a mean follow-up duration of 3.6 years (versus 8.10 years in our study). Nevertheless, their data do suggest that transmen receiving testosterone are at a higher risk for a MI. The greater occurrence of CVEs in transgender individuals may be explained in part by the effect of THT on cardiovascular risk factors such as lipid levels.<sup>1</sup> A limitation of our study is that we could not adjust for potential confounders such as psychosocial stressors and smoking (of which the prevalence was relatively high in our population: 43%–46%) because of our study design. In addition, we used a different method for the assessment of CVEs than the reference studies did (screening medical files versus using registries). Furthermore, the risk of CVEs has decreased over time. Although we tried to take this secular trend into account by comparing the rates of our study with published rates between 1972 and 2015,<sup>2–4</sup> we cannot exclude that this limitation, in addition to the different assessment method, has affected our SIRs.

Considering the limitations, we conclude that the incidences of strokes and VTEs are higher in transwomen

receiving THT than in both reference women and men. In addition, transwomen and transmen receiving THT are at higher risk of MIs than reference women. Both physicians and transgender individuals should be aware of these risks, and risk factors should be adequately managed.

## ARTICLE INFORMATION

Data sharing: All data supporting our findings are available in the article or from the corresponding author on reasonable request.

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## Disclosures

None.

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