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RESEARCH ARTICLE

Cardiovascular Disease Risk Estimation for Transgender and Gender-Diverse Patients: Cross-Sectional Analysis of Baseline Data From the LITE Plus Cohort Study

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Introduction: Approximately 2% of the U.S. population identifies as transgender, and transgender people experience disproportionate rates of cardiovascular disease mortality. However, widely used cardiovascular disease risk estimators have not been validated in this population. This study sought to determine the impact on statin therapy recommendations using 3 different approaches to operationalizing sex in the American Health Association/American College of Cardiology Pooled Cohort Equation Risk Estimator.

Methods: This is a cross-sectional analysis of baseline clinical data from LITE Plus, a prospective cohort study of Black and/or Latina transgender women with HIV. Data were collected from October 2020 to June 2022 and used to calculate Pooled Cohort Equation scores.

Results: The 102 participants had a mean age of 43 years. A total of 88% were Black, and 18% were Latina. A total of 79% were taking gender-affirming hormones. The average Pooled Cohort Equation risk score was 6% when sex assigned at birth was used and statins would be recommended for the 31% with Pooled Cohort Equation >7.5%. The average risk score was 4%, and 18% met the criteria for statin initiation when current gender was used; the mean risk score was 5%, and 22% met the criteria for statin initiation when current hormone therapy was used.

Conclusions: Average Pooled Cohort Equation risk scores vary substantially depending on the approach to operationalizing the sex variable, suggesting that widely used cardiovascular risk estimators may be unreliable predictors of cardiovascular disease risk in transgender populations.

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Collection of sex, gender, and hormone use in longitudinal studies of cardiovascular health is needed to address this important limitation of current risk estimators.

INTRODUCTION

Cardiovascular disease is a leading cause of death among transgender and/or gender-diverse people (TGD). A 30-year retrospective cohort study of adult transgender people on hormone therapy in Amsterdam found elevated cardiovascular disease-related mortality, with standardized mortality ratios as high as 2.6 among transgender women compared with those among cisgender women.[1] In the U.S., approximately 2% of the adult population identifies as TGD.[2] TGD people face a higher prevalence of poor cardiovascular health driven by intersecting structural, psychosocial, and biomedical factors.[3] Structural factors include high rates of unemployment and poverty—rooted in discrimination—that reduce access to medical care. Psychosocial stressors caused by pervasive stigma increase allostatic load and cardiovascular risk.[4] Some studies suggest that exogenous hormones used for gender affirmation may also affect cardiovascular risk.[5,6] Cardiovascular disease risk is elevated among people with HIV[7] and may be particularly high for TGD people with HIV.[8]

Primary prevention of cardiovascular events includes statin therapy, which comes with potential adverse effects, such as myopathy.[9] Atherosclerotic cardiovascular disease (ASCVD) risk estimators facilitate clinical decision making about when the risk for a negative ASCVD event is high enough to start statin therapy.[10] These estimators use statistical algorithms to calculate the 10-year and lifetime risks. The current American Heart Association/American College of Cardiology Risk Estimator utilizes the Pooled Cohort Equation (PCE) ASCVD Risk Assessment tool to assess 10-year risk.[11] The PCE and other tools base their estimates on modifiable risk factors such as tobacco use, hypertension, and diabetes mellitus as well as personal characteristics such as race and sex. Statin initiation is considered when the risk score reaches or exceeds 7.5%.[9–11]

ASCVD risk estimators are standardized and convenient. However, they have important shortcomings, especially for TGD populations. Their algorithms operationalize sex as either male or female. Clinicians caring for TGD patients whose gender identity, anatomy, and/or hormone profile differ from what is expected by this binary are left without evidence-informed guidance.[5,12] How should clinicians account for types, doses, and duration of gender-affirming hormone therapy (GAHT); duration of exposure to endogenous sex hormones (e.g., from puberty until the start of GAHT); interruptions in GAHT over time; and the impact of gender-affirming gonadal surgeries? The objective of this analysis was to examine the clinical consequences of different approaches to operationalizing the sex variable in the ASCVD risk calculators, with a focus on individuals living with HIV—who face an elevated risk for cardiovascular disease. We used the PCE estimator to calculate ASCVD risk for a cohort of transgender women on the basis of 3 different interpretations of sex: (1) sex assigned at birth, (2) current gender identity, and (3) current GAHT use.

METHODS

Study Sample

Data were drawn from LITE Plus, an ongoing, multisite, U.S.-based observational study that follows a prospective cohort of transgender women. Protocol details have been previously published.[13] In brief, eligibility included reporting male sex assigned at birth and current binary female and/or feminine gender identity; age ≥18 years; laboratory-confirmed HIV; self-identity as Black and/or Latina; ability to communicate in English or Spanish; and residence in 1 of 3 cities where data collection would take place: Washington, DC; New York, NY; and Boston, MA. The convenience sample was recruited using community outreach, clinic flyers, and social media. The University of North Carolina School of Medicine IRB approved the study (IRB Number 18-2362).

Measures

The study collects semiannual interviewer-administered surveys as well as annual clinical measures and laboratory biomarkers of cardiovascular health and chronic stress. For this analysis, we used baseline data collected from October 2020 to June 2022. Measures included self-reported age, race, ethnicity, smoking history, diabetes diagnosis, and current medications; clinical measures of systolic and diastolic

blood pressure; and laboratory results for lipid profile and HbA1c. Descriptive statistics and PCE scores were calculated using R Statistical Software (Version 4.1.2, R Core Team 2021).[14] The algorithm for the PCE is available online at ClinCalc.com.[11,15]

Statistical Analysis

Descriptive statistics and PCE scores were calculated using R Statistical Software (Version 4.1.2, R Core Team 2021).[14] The algorithm for the PCE is available online at ClinCalc.com.[11,15]

RESULTS

The average age of study participants was 43 years. The vast majority self-identified as Black (88%), and 18% identified as Latina. Almost all participants (97%) reported being on antiretroviral therapy. GAHT use was common: 91% of participants had ever taken GAHT, and 79% were currently taking it. Dyslipidemia was common, with 46% of the participants having a low-density lipoprotein ≥100 mg/dL. Other common risk factors included current (30%) or former (25%) cigarette smoking, self-reported diabetes (12%), and elevated systolic (17%) or diastolic (13%) blood pressure. More than 1 in 5 (23%) were taking an antihypertensive medication, 19% were taking a statin, and 9% were taking daily aspirin (Table 1).

The average 10-year risk of an ASCVD event was 6% when sex assigned at birth (male) was used in the algorithm. Using the PCE score cut off of 7.5%, statins would be recommended for 31% of participants using this approach. When the PCE score was calculated using current gender identity (female), the mean risk score fell to 4%, and only 18% met the criteria for statin initiation. When scores were calculated using female for participants who were taking GAHT at the time of their visit and male for participants who were not taking GAHT, the mean risk score was 5% for the overall sample, and 22% met the criteria for statin initiation.

Table 1. Cardiovascular Risk and Risk Factors for Black and Latina Transgender Women With HIV, the LITE Plus Study

Variables	Summary statistics
Characteristics, N=102	
Age in years	
Mean (range)	43 (21–71)
≥40 years, *n* (%)	55 (54)
Race and ethnicity	
Black of any ethnicity, *n* (%)	90 (88)
Latina of any race, *n* (%)	18 (18)
Black and Latina, *n* (%)	7 (7)
GAHT	
Ever taken GAHT, *n* (%)	93 (91)
Currently taking GAHT, *n* (%)	81 (79)
Currently taking antiretroviral therapy, *n* (%)	99 (97)
ASCVD risk scores, N=101	
ASCVD risk score (all assigned male)	
Mean (IQR)	6 (2–10)
≥7.5, *n* (%)	31 (31)
ASCVD risk score (all assigned female)	
Mean (IQR)	4 (0.2–6)
≥7.5, *n* (%)	18 (18)
ASCVD risk score (assigned female if on GAHT)	
Mean (IQR)	5 (0.3–6)
≥7.5, *n* (%)	22 (22)
CVD risk factors	
Systolic blood pressure	
Mean (IQR)	126 (116–134)
≥140 mmHg, n/N (%)	17/102 (17)
Diastolic blood pressure	
Mean (IQR)	81 (75–86)
≥90 mmHg, -n/N (%)	13/102 (13)
Total cholesterol	
Mean (IQR)	175 (146–193)
≥200 mg/dL, n/N (%)	23/102 (23)
HDL	
Mean (IQR)	54 (43–62)
≤40 mg/dL, n/N (%)	17/101 (17)
LDL	
Mean (IQR)	99 (76–118)
≥100 mg/dL, n/N (%)	46/101 (46)
Diabetes	
Self-report, n/N (%)	12/102 (12)
HbA1c≥6.5, n/N (%)	10/101 (10)
Current smoker, n/N (%)	31/102 (30)
Former smoker, n/N (%)	26/102 (25)
On antihypertension medication, N/*n* (%)	23/102 (23)
On aspirin, n/N (%)	9/102 (9)
On statin, n/N (%)	19/101 (19)

ASCVD, atherosclerotic cardiovascular disease; GAHT, gender-affirming hormone therapy; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

DISCUSSION

The differences in the proportion of participants who would be recommended for statin therapy on the basis of various approaches to the sex variable highlight the limitations of current ASCVD risk estimators. Binary operationalization of sex as male or female does not reflect the true complexity of sex or gender. Gender diversity is well documented and has multiple implications for health, including ASCVD risk.[3,16] Sex is a multidimensional construct that includes a variety of hormones, anatomical structures, and chromosomal configurations that vary within and across individuals with the same assigned sex at birth.[17] Therefore, it is unclear what the sex variable in the risk estimator actually represents and how a clinician should select from the binary options when patients do not fit typical categories.

ASCVD risk estimators with binary sex options may fail to accurately characterize the risk in TGD populations as well as other groups, such as people with differences in sex development, postmenopausal cisgender women (taking or not taking exogenous hormones), and cisgender men with hypogonadism. Invalid risk estimates may limit informed decision making about the risk-benefit of statin use. Underestimates of risk may result in failures to intervene before preventable cardiovascular events, whereas overestimates of risk may expose patients to unnecessary adverse effects from statin therapy. The consequences of overestimation or underestimation of risk may be particularly salient for TGD people with HIV, whose ASCVD risk may be affected by HIV disease, antiretroviral therapy, hormone therapy, and gender minority stress.

More complete longitudinal data are needed to inform ASCVD risk estimation and shared decision making.[18] Most existing longitudinal studies of cardiovascular health do not specifically recruit gender-diverse populations nor do they collect specific sex characteristics (e.g., hormone levels, anatomy) or gender identity data. This erasure of sex and gender complexity precludes opportunities to inform future clinical tools that could accurately assess risk in TGD populations known to experience a greater burden of ASCVD mortality. Inclusion of sex and gender identity measures and more detailed information about hormone status is urgently needed in longitudinal ASCVD research.

Limitations

Although often used for younger populations, the PCE has been validated for adults aged ≥40 years. The study was not designed to capture ASCVD events; therefore, we cannot determine the predictive value of any existing risk estimator. However, our data highlight the need for further research to improve primary ASCVD prevention among TGD adults.

CONCLUSIONS

Widely used ASCVD risk estimators may be unreliable predictors of risk in TGD populations. Collection of sex, gender, and hormone use in longitudinal studies of cardiovascular health is needed to address this important limitation of current risk estimators.

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Declaration of interest: TP serves as a research consultant for studies conducted by ViiV Healthcare. CGS serves as a consultant for EverlyWell.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.focus.2023.100096.

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