Characteristics of Transgender Women Referred to Women's Heart Clinic ☆

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ABSTRACT

Introduction: Transgender women have been reported to have a high burden of cardiovascular disease (CVD) and risk factors based largely on surveys. Our aim was to describe the prevalence of CVD and associated comorbidities among a cohort of older transgender women referred to cardiology as part of their gender-affirming care.

Methods: This was a retrospective, cross-sectional study of transgender women at a single institution from 2017 to 2019.

Results: Fifty-two consecutive patients were included. The most common reasons for referral were cardiac risk factor management (45%) and pre-operative cardiac risk stratification prior to gender-affirming surgery (35%). The mean age was 57 ± 10 years, 87% were white, and 92% had insurance coverage. Forty-eight patients (92%) were taking gender-affirming hormone therapy; 5 had undergone breast augmentation, 4 had undergone orchiectomy, and 2 had undergone vaginoplasty. The most common comorbidities were depression and/or anxiety (63%), obesity (58%), and hyperlipidemia (54%). Excluding aldosterone antagonists, 46% were on cardiac medications; changes were recommended for 25% of patients: new prescriptions in 9, dose adjustments in 5, and discontinuations in 4. According to the pooled cohort equation, the 10-year risk of atherosclerotic CVD was $9.4 \pm 7.7\%$ when the study population was calculated as male and $5.2 \pm 5.1\%$ when calculated as female ($p < 0.001$). For patients who completed exercise testing, the functional aerobic capacity was fair ($77.6 \pm 21.4\%$) when calculated as male and average ($99.5 \pm 27.5\%$) as female ($p < .0001$); there was inconsistency in sex used for calculating the result on the formal report.

Conclusions: Older transgender women may have an underestimated prevalence of CVD and its risk factors. More research is needed to identify cardiovascular health profiles, improve practice consistency, and establish normative values for transgender patients.

1. Introduction

Transgender and gender diverse (TGD) adults face a myriad of healthcare challenges, including access to consistent care by medical providers with appropriate expertise; management of cardiovascular disease (CVD) in this population is no exception. Multiple studies have reported a disproportionate burden of CVD and its risk factors among TGD patients, especially among transgender women. [[1–4]] However, these reports are often limited by selection bias and reliance on self-reported or subjective variables and skew toward young individuals. [1,2,5–8] Moreover, the evolution of gender-affirming hormone therapy (GAHT) away from use of ethinyl estradiol renders some published data outdated, such that the risk of hard outcomes of CVD conferred by

GAHT in older TGD individuals is unknown. [3,9–11] Thus, recommendations put forward by medical societies rely heavily on expert opinion and extrapolation from the cisgender population. [12 14] For example, regular screening for cardiac risk factors and metabolic changes in transgender persons treated with GAHT is recommended by clinical practice guidelines. [13] However, treatment thresholds and targets have not been defined.

There is an urgent need for objective data to guide clinical and treatment decisions, combat existing healthcare outcome disparities, and improve education for medical providers on the specific considerations for the TGD population.

The primary aim of this study is to describe the cardiovascular health of a cohort of older transgender women referred to Women's Heart Clinic

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(WHC) using objective parameters from the electronic medical record. Additionally, we sought to examine the impact of involving cardiologists in coordinated, multi-disciplinary care.

2. Methods

This was a retrospective, observational, cross-sectional study of transgender women at a single tertiary care center. At our institution, patients interested in GAHT or gender-affirming surgery are initially seen in the endocrinology Transgender and Intersex Specialty Care Clinic, where the appropriateness of and readiness for intervention is assessed. Additional referrals are made, including to psychiatry, social work, cardiology, or additional subspecialty care as indicated. The endocrinologists specializing in TGD care coordinate these referrals and integrate recommendations. Many patients are already on GAHT at the time of arrival to our institution.

The WHC began seeing patients in November of 1998 and now has become the referral destination of transgender women needing cardiac care. Patients included in this study were identified by searching referral records from endocrinology between January 2017 and December 2019; cisgender women were excluded.

Manual chart review for data abstraction were performed on all included patients. Variables of interest included demographic data, medical and social histories, and results of blood tests, electrocardiograms, echocardiograms, exercise treadmill tests, nuclear myocardial perfusion tests, and coronary artery calcium scores. Scores with sex-specific variables were calculated twice, once as male and once as female. Likewise, the 10-year risk of atherosclerotic cardiovascular disease was calculated as both male and female. [15]

This retrospective study was approved by the Institutional Review Board and is in accordance with Minnesota Research Authorization.

2.1. Definitions

Gender identity is reported here as described and self-defined by each patient; our use of the terms "sex" or "biologic sex" is based on genetic and anatomic factors. Gender is not dictated by nor does it imply the use of GAHT, a history of gender-affirming surgery, or pronoun preference. Therefore, transgender women are those who are biologically categorized as male sex but identify as female gender. The term "cisgender" refers to people whose gender identity corresponds to his or her biologic sex.

Because of charting limitations, tobacco use and alcohol use were dichotomized as either current or prior regular use or as never used. Cardiovascular disease was defined as patients with previously documented coronary artery disease requiring revascularization, moderate or severe valve disease, history of valve repair or replacement, or previously diagnosed cardiomyopathy or heart failure.

3. Results

Fifty-two consecutive transgender women were referred to the WHC during the specified period, 16% of the transgender women who presented for Transgender and Intersex Specialty Care Clinic consultation. The mean age was 57 ± 10 years; 87% self-identified as white. The most common reasons for cardiology referral according to endocrinology documentation were management of cardiac risk factors (45%) or known cardiovascular disease (23%), pre-operative risk assessment prior to gender-affirming surgery (35%), and/or evaluation of symptoms concerning for coronary disease (6%). Some patients had multiple indications for referral. Female gender was documented in the medical chart for 90% of patients. Twenty-nine patients (56%) had Medicare and/or Medicaid insurance, 19 (37%) were covered by private insurance, and 4 (8%) were uninsured. The most common comorbidities included depression and/or anxiety (63%), obesity (58%), hyperlipidemia (54%), alcohol use (51%), chronic lung disease (38%), and tobacco use (35%);

1 patient (2%) had a history of venous thromboembolism. At the time of establishing cardiac care, 48 (92%) were taking GAHT; 87% were taking an estrogen preparation (38% transdermal, 27% oral, 21% injectable), 85% were on an aldosterone antagonist, and 27% were on progesterone. The average age at initiation of GAHT was 53 ± 13 years. Regarding surgical history, 5 patients had undergone breast augmentation, 2 had undergone vaginoplasty and orchiectomy, 2 had undergone orchiectomy alone, 1 had undergone facial feminization, and 1 had undergone a vocal cord procedure for voice feminization. Complete baseline characteristics are shown in Table 1.

Prior to cardiac consultation, 20 patients (38%) were already on statin therapy; no one was on a PCSK9 inhibitor. Regarding antiplatelet agents, 16 (31%) were on aspirin and no one was on an alternative antiplatelet agent. Four patients (8%) were on systemic anticoagulation with warfarin or a non-vitamin K oral anticoagulant because of atrial arrhythmia, presence of a mechanical heart valve, or a history of venous thromboembolism.

At the WHC visit, 25% of patients had adjustments to their cardiac medication regimen: 9 patients had new medications prescribed or recommended, 5 had dose adjustments, and 4 had one or more medications or supplements discontinued. Seven patients (13%) had ≥2 medication changes. The most common change was to start or escalate therapy for lipid management (statin therapy in 8 patients, ezetimibe in 2 patients). Aspirin was the second most common medication adjusted; it was started in 4 patients and discontinued in 2. Two patients had over-the-counter supplements discontinued.

3.1. Cardiovascular testing

The most common cardiac test ordered was an electrocardiogram (90% of the cohort), of which 34% were abnormal (Table 2). Information from transthoracic echocardiography was available in 79% of patients and showed normal mean left ventricular ejection fractions, left ventricular mass indices (according to male or female sex), left atrial volume indices, and estimated right ventricular systolic pressures. Five patients (12% of those tested) had at least moderate valve disease or history of valve intervention; 1 patient had resting regional wall motion abnormalities. Stress testing was ordered for 40 patients (77%) and was comprised of stress echocardiogram for 35 patients, nuclear perfusion imaging in 3, and a treadmill exercise test without imaging in 2 patients. Two patients (5% of those tested) had stress-induced ischemia, both of whom were referred for coronary angiography, and one of whom underwent percutaneous coronary intervention. For patients who completed exercise testing, the mean functional aerobic capacity (FAC) was fair ($77.6 \pm 21.4\%$) when calculated as male and average ($99.5 \pm 27.5\%$) as female ($p <. 0001$); there was inconsistency in sex used in the formal report. Of the 7 patients who had a coronary calcium score, 3 (43%) had detectable calcium. According to the pooled cohort equation, the 10-year risk of atherosclerotic CVD disease was $9.4 \pm 7.7\%$ when the study population was calculated as male and $5.2 \pm 5.1\%$ when calculated as female ($p < 0.0001$). [15]

4. Discussion

Cardiovascular health is affected by diverse factors beyond the traditional risk factors of age, sex, and tobacco use; recent guidelines from the American Heart Association and American College of Cardiology emphasize a patient-centered, team-based approach that evaluates the contributions from various sources such as genetics, comorbidities, lifestyle habits, and socioeconomics. [16] Mental illness and exposure to adversity are specifically and explicitly stated as risk factors that are not captured by commonly used CVD risk equations but are of particular relevance to the TGD community. Cardiovascular care of the TGD population is ideally provided with a comprehensive approach (Figure 1: Central illustration). This study of a select group of

Table 1
Baseline characteristics and comorbidities.

Baseline Patient Characteristics	n	%
Race/ethnicity		
White (non-Latinx)	45	87
Black	1	2
Latinx	1	2
Other	1	2
Unknown	4	8
Comorbidities		
Obesity (BMI $\geq$ 30 Kg/m^2)	30	58
Hyperlipidemia	28	54
Hypertension	19	37
Diabetes mellitus	8	16
History of myocardial infarction and/or prior revascularization	2	4
Depression and/or anxiety	33	63
Tobacco use	18	35
Alcohol use	26	51
Recreational drug use	10	19
Asthma or chronic obstructive pulmonary disease	20	38
Obstructive sleep apnea	16	31
Thyroid disease	9	17
Family history of premature coronary artery disease	5	10
Chronic kidney disease $\geq$ stage 3	4	8
Atrial fibrillation or flutter	2	4
Prior cerebrovascular accident or transient ischemic attack	2	4
History of venous thromboembolism	1	2
Heart failure	1	2
Peripheral arterial disease	1	2
Pulmonary hypertension	1	2
Human immunodeficiency virus infection	0	0
Medications		
Statin	20	38
Aspirin	16	31
Beta blocker	8	16
Diuretic	7	13
Angiotensin converting enzyme inhibitor or angiotensin receptor blocker	6	12
Calcium channel blocker	5	5
Anticoagulation	4	8
Insulin	3	6
Non-insulin injectable or oral hypoglycemic agent	6	12
Gender-affirming hormone therapy (GAHT)		
Androgen antagonist	44	85
Estrogen	45	87
Transdermal Estradiol	20	38
Oral Estradiol	14	27
Injectable Estradiol	11	21
Progesterone	14	27
Status post orchiectomy	2	4
Status post vaginoplasty and orchiectomy	2	4
Status post breast augmentation	5	10

SD, standard deviation.

52 transgender women referred to cardiology as an integrated component of their gender-affirming care documented high rates of CVD and its risk factors. Moreover, cardiac consultation optimized the medical treatments of comorbidities even with high baseline rates of cardiac prescriptions, abnormalities discovered on routine cardiac testing did not preclude gender-affirming care, and sex-based calculations and reference ranges led to uncertainty in result interpretation in this population.

Consistent with other studies, our cohort had a high prevalence of traditional risk factors for cardiovascular disease such as obesity, hypertension, hyperlipidemia, and tobacco use. [7,17,18] Likewise, high rates of anxiety and depression were noted, both of which also have strong associations with CVD. [19–21] Mental illness may be related to risk factors that are more difficult to collect by chart review but nevertheless impact cardiovascular health, such as minority stress, health illiteracy, transportation barriers, and under-employment. [16] Most patients in this cohort had health insurance coverage, which is less common among TGD than cisgender adults. [2] This finding should be considered in the context of care in a state that fully expanded Medicaid by 2014. Additionally, this older cohort had more eligibility for Medicare and had demonstrated an ability to overcome barriers to appointments and testing. Although the preponderance of risk factors for CVD in this cohort was likely the cause for referral by endocrinology and does not reflect comorbidity rates in all-comers, it is possible that high rates of risk factors excluded in common calculators and difficult-to-measure social determinants of health lead to underestimation of CVD risk in transgender women.

4.1. Anticipated impacts of feminizing hormone therapy

A major finding of this study is that even transgender women with access to subspecialty medical care had room for optimization of their cardiac medical regimens. Excluding spironolactone, 24 (46%) of patients were already on cardiovascular medications at the time of consultation, most commonly lipid-lowering therapy. Some metabolic changes can be anticipated with GAHT and therefore should prompt preemptive medication adjustments as well as behavioral counseling. The effects of

Table 2
Results of initial cardiac testing.

Results of Testing at Index Visit		
Laboratory (mean ± SD)		
Hemoglobin A1c (%)	5.5 ± 1.4	
Total cholesterol (mg/dL)*	187 ± 50	
High-density lipoprotein (mg/dL)*	52 ± 14	
Low-density lipoprotein (mg/dL)*	99 ± 33	
Triglycerides (mg/dL) †	160 ± 129	
Creatinine (mg/dL) ‡	1.02 ± 0.18	
Resting electrocardiogram, *n* = 47 (90%)		
	n	%
Normal	31	66
First degree atrioventricular block	4	9
Left ventricular hypertrophy	3	6
Sinus bradycardia	3	6
Sinus tachycardia	2	4
Nonspecific intraventricular conduction delay	2	4
Q waves/age-indeterminate infarction	2	4
Premature ventricular contraction(s)	2	4
Premature atrial contraction(s)	1	2
Right bundle branch block	1	2
Transthoracic echocardiography, *n* = 41 (79%) §		
Left ventricular ejection fraction (%), mean ± SD	61 ± 4	
Left ventricular mass index (g/m^2), mean ± SD	80.6 ± 20.3	
Left atrial volume index (mL/m^2), mean ± SD	26 ± 8	
Estimated right ventricular systolic pressure, mean ± SD	26 ± 7 mmHg	
≥Moderate valve disease, n (%)	5 (12)	
Resting regional wall motion abnormalities, n (%)	1 (2)	
Stress testing‖		
Male functional aerobic capacity (%), mean ± SD	78 ± 21	
Female functional aerobic capacity (%), mean ± SD	100 ± 28	
% predicted maximum heart rate, mean ± SD	92 ± 9	
Double product, mean ± SD	24,347 ± 4982	
Positive electrocardiographic changes, n (%)	0 (0)	
Positive imaging changes, n (%)	2 (5)	
Coronary calcium score, *n* = 7 (14%)		
Undetectable, n (%)	4 (57)	
Detectable calcium, n (%)	3 (43)	
Percentile range according to male sex	37–88	
Percentile range according to female sex	56–97	

SD, standard deviation.

* To convert to mmol/L, multiply by 0.02586.

† To convert to mmol/L, multiply by 0.01129.
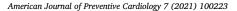
‡ To convert to μmol/L, multiply by 88.4.

§ Includes rest images obtained at the time of stress echocardiography.

‖ Stress echocardiogram in 35, nuclear perfusion test in 3, treadmill exercise test in 2.

Fig. 1. Central illustration: Factors impacting cardiovascular care of transgender women.

[5] Coadministration of progestins and anti-androgens may be the cause of some conflicting results, and more data are needed before conclusions can be drawn. [27]

Limited observational data are available for other cardiovascular risk factors. Changes in body composition on GAHT may be responsible for weight gain and loss of muscle mass; [27,30] insulin resistance may also be adversely affected. [30,31] The minimal decrease in blood pressure noted in some studies is unlikely to be of clinical significance. [27,32]

To what degree biomarkers correlate with meaningful cardiovascular outcomes is a distinct, and perhaps more important, question. Several studies have reported higher rates of myocardial infarction in transgender women than cisgender women but similar to cisgender men when adjusting for risk factors. [3,7] This similarity is the basis for our practice of interpreting test results and risk stratifying according to biologic sex. Ischemic stroke is a unique case and appears to be more prevalent among transgender women than either cisgender men or women. [3,4] More research is needed in this area to elucidate the drivers of this concerning trend and guide clinical response.

Notably, the use of GAHT has been associated with improvement in other health metrics such as increased physical activity and better mental health. [14,27] Beneficial effects on other healthcare domains have been reported when transgender women utilize transition-related medical services. [8] Multidisciplinary collaboration may be a unique opportunity for a comprehensive assessment of risks, tracking outcomes, and development of an appropriate treatment strategy.

4.2. Cardiovascular testing

Routine cardiac testing revealed a high percentage of abnormal results, none of which precluded continuing gender-affirming care. The influence of GAHT over time has been studied for common laboratory values, but long-term changes with respect to other types of testing are unknown and worthy of further investigation.

Finally, there was uncertainty applying appropriate reference ranges for sex-based test results, including coronary artery calcium scores, functional aerobic capacity, and some echocardiographic parameters. Sex is also a component of the commonly used pooled-cohort equation to estimate 10-year atherosclerotic CVD risk. [15] In these calculations,

GAHT on risk factors for cardiovascular disease depend on the regimen chosen and the routes of administration.

The increase in thrombotic risk associated with exogenous estrogen administration has been reported in both transgender and cisgender women. Data on thrombotic events on feminizing hormone therapy is complicated by differences in hormone formulations, routes of administration, and doses; prescribing patterns have changed considerably over time. [22] There is data in both transgender and cisgender women to suggest some degree of increased rate of venous thromboembolism on feminizing hormone therapy. [23,24] Of particular importance to our cohort, risk of thrombosis may increase over time. Providers should be particularly mindful of this when treating older TGD, as age confers additional risk for thrombosis on top of decades of estrogen administration. [25] While head-to-head dose-equivalent trials are not available, the transdermal route is generally favored for its safety profile and is our current practice, especially in women at increased risk. [23,26]

As in assessment of thrombotic risks, the effects of GAHT on lipid panels are difficult to summarize due to study and treatment heterogeneity. One study showed a decrease in LDL, HDL, and triglycerides, [27] whereas other studies have shown no significant difference, [28] an effect on HDL alone, [29] or a significant change in triglycerides alone.

incorporation of female sex may lead to underestimating risk and over-estimating fitness. Inconsistent application of reference ranges and un-known normative values can lead to uncertainty in test interpretation. At our institution, we have added the statement to stress test reports for TGD patients "Normal ranges reported may not be applicable in this case due to specific patient characteristics" to draw providers' attention to this area of uncertainty. Test results indexed to body surface area, including many echocardiographic parameters, may have an advantage in this setting. As in cancer screening recommendations for TGD persons, biologic sex should play a significant role in cardiovascular care and risk stratification. [13]

5. Limitations

The cohort in this study sought gender-affirming care at a single institution and was generally older and less racially diverse than reported by population-based surveys; therefore, our findings may not be generalizable to the entire population of transgender women. The cohort reported includes only the 16% of the transgender women that were referred to cardiology. Moreover, these women were at different stages of their gender transition without uniformity in GAHT dosing or formulations. This study does not establish normative reference values for transgender women; for example, in most cases, baseline lipid panels prior to the initiation of any lipid-lowering therapy were not available. Finally, it does not explore reasons for prevalence of CVD or comorbid conditions.

6. Conclusions

The prevalence of CVD and its risk factors may be underestimated in older transgender women. More research is needed to identify the specific needs of transgender patients as well as to establish normative values. Accessing care for GAHT may provide a gateway to a team approach for management of CVD and risk factor reduction.

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Disclosures

None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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