

# Study: Cardiac biomarkers in transgender people

## Charna Albert

February 2023—Sex hormones, rather than sex assigned at birth, may be a stronger driver of the observed concentration differences between healthy men and women for biomarkers of cardiac disease, say the authors of a study published in *JAMA Cardiology* (Greene DN, et al. *JAMA Cardiol.* 2022;7[11]:1170–1174).



Dr. Greene

The aim of their cross-sectional prospective study was to determine the distribution of high-sensitivity cardiac troponin (hs-cTn) and N-terminal pro-brain natriuretic peptide (NT-proBNP) in healthy transgender people who were prescribed testosterone or estradiol for 12 months or more. Seventy-nine transgender men and 93 transgender women were recruited for the study between late 2017 and mid-2018 from internal medicine and primary care clinics that specialize in transgender medical care.

The study found that concentrations of hs-cTn were higher in transgender men than in transgender women. For Abbott hs-cTnI, the authors report, the median concentration observed in transgender men and women was 0.9 (0.6–1.7) ng/L and 0.6 (0.3–1.0) ng/L, respectively. Results were consistent across two additional hs-cTn assays from Beckman Coulter (hs-cTnI) and Roche (hs-cTnT). The median NT-proBNP concentration was significantly higher in transgender women (49 [32–86] ng/L) than in transgender men (17 [13–27] ng/L).

“Seeing the distribution of relative results in the cohort of transgender men and women be so consistent between the three [troponin] assays was surprising to me,” says study coauthor Dina N. Greene, PhD, D(ABCC), clinical associate professor, University of Washington, and associate laboratory director, LetsGetChecked. These results were particularly unusual for a study measuring low concentrations of cardiac troponin in healthy people, Dr. Greene says, noting that lack of standardization or harmonization of cardiac troponin assays usually has an effect. “That’s not to say the cohorts are perfect and this is the be-all, end-all, but it was an encouraging way for me to feel comfortable presenting the data as it is.”

Study participants were a range of ages, used different methods of hormone administration, and had been on gender-affirming hormone therapy for varying lengths of time (mean of 4.8 years for transgender men and 3.5 for transgender women). “The heart doesn’t remodel as quickly as you might think. That’s a couple years of hormone therapy. But clearly there is cardiac restructuring happening,” she says. The duration needed to show changes in hs-cTn and NT-proBNP concentrations remains unknown, the study says.

Dr. Greene and coauthors note in the study that systematic reviews indicate that the hs-cTn concentration differences observed between the sexes lead to differing 99th percentile upper reference limits, and that some clinical guidelines stress the importance of using sex-specific decision points. Though the study was a pilot only—“these were cardiac healthy people,” Dr. Greene says, “and we weren’t powered strongly enough to have 99th percentiles derived from this study”—the initial data suggest that when sex-specific 99th percentiles are used, the numeric value associated with affirmed gender, rather than sex assigned at birth, may be the appropriate upper reference limit.

These results, she says, highlight the importance of serial troponin measurements. Any patient with an initial measurement below the male-specific 99th percentile but above the female-specific 99th percentile should have a

second measurement taken, she says, “but for a transgender man it’s even more important that you get that serial measurement, because you don’t know which 99th percentile is appropriate. Should you have used the female or the male? In transgender people it’s even more important to follow the standards of care for getting a serial troponin measurement when trying to distinguish between acute myocardial infarction and other reasons for chest pain, or other symptoms that often are associated with acute myocardial infarction.”

The impact of the sex hormones on the physiological mechanism that accounts for the sex-based difference in hs-cTn concentrations is an area for further study. “I would love to see heart imaging...before and after taking gender-affirming hormones,” Dr. Greene says. “Understanding the anatomical changes that happen would help us better understand the physiological measurements we’re seeing.”

Dr. Greene and her colleagues report that transgender women have a distribution of NT-proBNP concentrations similar to that of cisgender women, and that transgender men trend similarly to cisgender men. “These differences,” they write, “do not lead to distinct sex-specific NT-proBNP diagnostic thresholds owing to the significant concentration elevations in overt heart failure and cardiovascular disease but likely signify the importance of sex hormone concentrations in cardiac metabolism.” The data as a whole indicate, Dr. Greene says, that “the sex differences that we see in the cardiac biomarkers have a sex hormone component.”

“It all trends together. Troponin concentrations increasing in trans men and NT-proBNP decreasing is exactly what we see in cisgender men, relative to cisgender women. It completes the package with these common biomarkers that we study.”

The observed differences in hs-cTn and NT-proBNP concentrations between cisgender women and transgender men, and cisgender men and transgender women, suggest the possibility of adverse cardiac remodeling from gender-affirming therapy, Dr. Greene and coauthors write, “but the clinical implications of the small differences remain unclear and deserve further study.” The study’s findings do not suggest that those who could benefit from gender-affirming hormone therapy need to consider potential adverse cardiac consequences, Dr. Greene says. “Nothing that changes in the heart based on gender-affirming hormone therapy could make me say there are adverse cardiac effects from using hormones, because the benefits of hormones are so important. Gender-affirming hormones save lives.”

Though some publications have illustrated that transgender people may have a slightly higher risk for some cardiovascular diseases, Dr. Greene and coauthors write, “the etiology is unclear and hard to differentiate from social determinants of health affecting the transgender population.” Similarly, they write, teasing out the clinical implications of sex-specific hs-cTn upper reference limits for ruling in acute myocardial infarction is complicated by biological and social factors that contribute to the poorer outcomes observed in women.

The socialization that leads to differences in clinical care “before that sample ever hits the lab” is important to understand, Dr. Greene says.

“By definition you cannot correct for the socialized bias that happens between individuals. You cannot correct for the way women and men handle symptoms differently because of the way they’ve been socialized about how much their pain matters,” she says. “I’m not saying we shouldn’t do the work—I’m saying we should do the work, and we should talk about how much these things matter first and foremost, in our discussion, in our results, and in our introductions, not as a single line as a limitation at the end of a discussion.”

*Charna Albert is CAP TODAY associate contributing editor.*