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Abstract

Aims The effects of inhibition of sodium glucose cotransporter (SGLT)-1, as opposed to SGLT2, on cardiovascular structure and function are not well known. We assessed the associations of a missense genetic variant of SGLT1 with cardiac structure and function.

Methods and results We evaluated associations of a functionally modifying variant of SLC5A1 (rs17683011 [p.Asn51Ser]), the gene that encodes SGLT1, with cardiac structure and function on echocardiography among middle-aged adults in the Coronary Artery Risk Development in Young Adults Study. Of 1904 participants (55.3 ± 3.5 years, 57% female, 34% Black), 166 (13%) White participants and 18 (3%) Black participants had at least one copy of rs17683011. There were no significant differences in age, sex, body mass index, glucose, or diabetes status by the presence of the rs17683011 variant. In Black participants, the presence of at least one copy of the rs17683011 variant was significantly associated with higher GLS compared with those without a copy of the variant after covariate adjustment (−15.8 ± 0.7% vs. −14.0 ± 0.1%, P = 0.02). Although the direction of effect was consistent, the association between the presence of at least one copy of rs17683011 and GLS was not statistically significant in White participants (−15.1 ± 0.2% vs. −14.8 ± 0.1%, P = 0.16). There were no significant associations between rs17683011 and other measures of LV structure, systolic function, or diastolic function.

Conclusions The rs17683011 variant, a functionally modifying variant of the SGLT1 gene, was associated with higher GLS among middle-age adults. These exploratory findings require further validation and suggest that SGLT1 inhibition may have beneficial effects upon LV systolic function.

Keywords Sodium-glucose cotransporter 1; Heart failure; Genetics; Echocardiography; Subclinical

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Introduction

While sodium-glucose co-transporter (SGLT) 2 inhibitors have emerged as foundational therapies to mitigate cardiovascular risk in high-risk individuals with diabetes and certain individuals without diabetes, less is known regarding the cardiovascular effects of SGLT1 inhibition.1,2 SGLT1 is primarily expressed within intestinal epithelial cells and is also expressed by left atrial (LA) and left ventricular (LV) cardiomyocytes. In murine models, SGLT1 appears to mediate oxidative stress in myocardial ischemia and SGLT1 overexpression leads to cardiac dysfunction, suggesting that inhibition of SGLT1 may provide cardiovascular benefit.3,4 Recently, the dual SGLT1 and SGLT2 inhibitor sotagliflozin has demonstrated reduction in cardiovascular events, including hospitalizations for heart failure (HF), among individuals with diabetes and either worsening HF or chronic kidney disease.5–7 However, murine models suggest dual SGLT1/2 inhibition may exacerbate cardiac dysfunction following myocardial infarction.8 In sum, the unique effects of SGLT1 inhibition, as opposed to SGLT2 inhibition, upon cardiovascular structure and function are unclear.
Genetic variation in sodium glucose co-transporter 1 and cardiac structure and function at middle age

One method to evaluate the long-term effects of SGLT1 inhibition on cardiac structure and function may be through genetic variants. Functionally damaging missense variants in SLC5A1, the gene that encodes SGLT1, are associated with metabolic benefits that may vary in effect size by race. However, the association of genetic variation in SLC5A1 with cardiovascular structure and function in later life is unknown, and such information may provide insight into potential mechanisms of cardiovascular benefit of SGLT1 inhibition. Therefore, we aimed to assess the associations of missense genetic variants of SGLT1 with echocardiographic measures of cardiac structure and function in later life among individuals in the Coronary Artery Risk Development in Young Adults (CARDIA) study.

Methods

Study population

The CARDIA study is a longitudinal cohort designed to study determinants of cardiovascular disease. A total of 5115 Black and White young adults (aged 18–30 years at baseline) without cardiovascular disease were initially recruited. Further details surrounding CARDIA study recruitment and protocol can be found in the supporting information and have been previously described. For this analysis, participants with genetic data and echocardiography at Year 30 examination were included. Of the 5115 participants, 2573 did not have genetic data available, and of the remaining 2542, 638 did not have echocardiography data, leaving 1904 participants for final analyses. The CARDIA study has been continuously approved by the institutional review boards at each of the four sites, and all participants provided written informed consent. The study is in line with the Declaration of Helsinki.

Genotyping and selection of single nucleotide polymorphisms of SLC5A1

We identified missense variants of SLC5A1 through a query of the publicly available National Human Genome Research Institute Genome Wide Association Studies catalogue. Within the catalogue, there were three single nucleotide polymorphisms (SNPs) of SLC5A1: rs17683011, rs17683430, and rs9609429. rs17683011 (p.Asn51Ser) and rs17683430 (p.Ala411Thr) are missense variants that have been associated with increased levels of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulino tropic polypeptide, which are incretins that stimulate insulin secretion. Because these variants are in linkage disequilibrium (R² = 1.0 in both Black and White participants), only rs17683011 was selected for further analysis. As the rs9609429 variant does not result in nonsynonymous amino acid substitution, it was not included for analysis.

Genotyping was performed separately in White and Black participants using the Affymetrix GenomeWide Human 6.0 array (Thermo Fisher Scientific). Principal component analysis was performed using EIGENSTRAT. Full details regarding genotype imputation can be found in the supporting information.

Echocardiography

The CARDIA echocardiographic protocol has been described previously and can be found in the supporting information. Two-dimensional, Doppler, and speckle-tracking echocardiography was performed among participants who attended the Year 30 examination. Echocardiographic outcome variables of interest included LV mass index, indices of LV systolic function (ejection fraction, global longitudinal strain [GLS], and circumferential strain), and indices of LV diastolic function (septal e' tissue velocity and E/e' ratio).

Statistical analysis

As part of a pre-specified analysis plan, we stratified all analyses by self-identified race group to eliminate potential confounding of results due to variants in linkage disequilibrium with rs17683011 that may vary across race. We compared clinical characteristics at Year 30 by the presence of at least one copy of rs17683011 using the χ² test for categorical variables and Student’s t-test for continuous variables. Linear regression models were used to evaluate associations of at least one copy of rs17683011 with indices of LV structure and function. Models were adjusted for age (at Year 30), sex, and genetic ancestry (principal components 1–3). In sensitivity analysis evaluating associations of rs17683011 with LV GLS, we additionally adjusted for body mass index (BMI) at Year 30. We assessed whether the presence of diabetes at Year 30 modified the association of the rs17683011 variant with LV GLS through interaction testing. Two-sided P-values of <0.05 were considered statistically significant. All analyses were performed using SAS version 9.4 (Cary, NC).

Results

Among the analytic cohort (mean age 55.3 ± 3.5 years), 1094 (57%) were female, and 642 (34%) were Black. Overall, 166 (13%) White participants and 18 (3%) Black participants had one or two copies of the rs17683011 variant. Of these, three White participants and one Black participant were homozygotes for rs17683011. There were no significant differences
in clinical characteristics by the presence of one or more copy of rs17683011, including systolic blood pressure, fasting glucose, body mass index, or LDL-cholesterol (Table 1). By Y30 exam, 19 participants (1%) developed HF. In Black participants, the presence of one or more copy of rs17683011 was significantly associated with better GLS after covariate adjustment (15.8 ± 0.7% vs. 14.0 ± 0.1%, P = 0.02) (Table 2; Figure 1). Although the direction of effect was consistent, the association between one or more copy of rs17683011 and GLS was not statistically significant in White participants (15.1 ± 0.2% vs. 14.8 ± 0.1%, P = 0.16) (Table 2). In sensitivity analysis further adjusting for BMI at Year 30, the association between rs17683011 and LV GLS was consistent in Black participants (15.8 ± 0.7% vs. 14.0 ± 0.1%, P = 0.02) and White participants (15.1 ± 0.2% vs. 14.8 ± 0.1, P = 0.14). There were no significant associations of the rs17683011 variant with other measures of LV structure (LV mass index), LV systolic function (LVEF), or diastolic function (e’ tissue velocities, E/e’) (Table 2). There was no interaction by diabetes status on the association of rs17683011 with GLS in Black participants (Pinteraction = 0.65).

**Discussion**

In a community-based cohort, we describe the association of a missense variant in the gene encoding SGLT1 with cardiovascular function at middle age. Despite a lower prevalence of rs17683011 carriers among Black participants compared with White participants, the rs17683011 variant was significantly associated with better LV GLS among Black participants. While the direction of effect of this association was consistent in White participants, the association did not reach

### Table 1 Characteristics of White and Black individuals at year 30 exam by presence of rs17683011

|                  | White participants |        |        |        | Black participants |        |        |
|------------------|-------------------|--------|--------|--------|-------------------|--------|--------|
|                  | Non-carrier (n = 1096) | rs17683011 heterozygote or homozygote (n = 166) | P-value | Non-carrier (n = 624) | rs17683011 heterozygote or homozygote (n = 18) | P-value |
| Age, years       | 55.8 ± 3.3         | 55.9 ± 3.3 | 0.59 | 54.4 ± 3.8         | 54.6 ± 4.5 | 0.82 |
| Female           | 586 (53)           | 101 (61) | 0.08 | 396 (61)           | 11 (61)   | 0.84 |
| BMI, kg/m²       | 28.7 ± 6.4         | 29.2 ± 6.5 | 0.40 | 32.4 ± 7.5         | 33.7 ± 8.4 | 0.46 |
| SBP, mmHg        | 116 ± 13           | 115 ± 15  | 0.44 | 124 ± 17           | 122 ± 13  | 0.61 |
| DBP, mmHg        | 71 ± 10            | 70 (10)   | 0.45 | 76 ± 11            | 76 ± 11   | 0.90 |
| LDL-c, mg/dL     | 112 ± 31           | 116 ± 32  | 0.09 | 107 ± 36           | 116 ± 33  | 0.34 |
| HDL-c, mg/dL     | 60 ± 19            | 62 ± 21   | 0.30 | 60 ± 18            | 59 ± 24   | 0.91 |
| Anti-hypertensive medication use | 233 (21) | 34 (20) | 0.82 | 292 (47) | 8 (44) | 0.84 |
| Diabetes         | 111 (10)           | 17 (10)   | 0.94 | 147 (24)          | 4 (22)    | 0.86 |
| Current smoker   | 96 (9)             | 10 (6)    | 0.26 | 103 (17)          | 3 (17)    | 0.77 |
| Education level, years | 16.1 ± 2.5 | 16.1 ± 2.5 | 0.99 | 14.4 ± 2.5 | 14.7 ± 2.0 | 0.58 |
| Fasting glucose, mg/dL | 99 ± 21 | 102 ± 35 | 0.32 | 102 ± 30           | 100 ± 20  | 0.75 |

BP, blood pressure; DBP, diastolic blood pressure; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SD, standard deviation.

Categorical variables are reported as n (%). Continuous variables are reported as mean ± SD.

### Table 2 Associations of rs17683011 (p.Asn51Ser) with cardiac structure and function by race

|                  | White participants |        |        |        | Black participants |        |        |
|------------------|-------------------|--------|--------|--------|-------------------|--------|--------|
|                  | Non-carrier (n = 1096) | rs17683011 heterozygote or homozygote (n = 166) | P-value  | Non-carrier (n = 624) | rs17683011 heterozygote or homozygote (n = 18) | P-value |
| LV structure     |                   |        |        |        |                   |        |        |
| LV mass index, g/m² | 78.1 ± 0.5       | 79.6 ± 1.4   | 0.30 | 82.0 ± 0.9      | 86.7 ± 5.3 | 0.39 |
| LV systolic function |                   |        |        |        |                   |        |        |
| LV ejection fraction, % | 60 ± 0.1       | 60 ± 0.4   | 0.51 | 59 ± 2.0        | 59 ± 1.4  | 0.84 |
| Global longitudinal strain, % | -14.8 ± 0.1   | -15.1 ± 0.2 | 0.16 | -14.0 ± 0.1     | -15.8 ± 0.7 | 0.02 |
| Circumferential peak strain, % | -14.5 ± 0.1   | -14.7 ± 0.3 | 0.57 | -14.4 ± 0.2     | -14.7 ± 1.0 | 0.73 |
| LV diastolic function |                   |        |        |        |                   |        |        |
| E/e’ ratio       | 7.6 ± 0.1         | 7.9 ± 0.2   | 0.10 | 8.3 ± 0.1       | 9.2 ± 0.6  | 0.13 |
| Doppler tissue septal e’ wave velocity, cm/s | 9.1 ± 0.1     | 9.1 ± 0.2   | 0.77 | 8.8 ± 0.1       | 9.1 ± 0.5  | 0.62 |

LV, left ventricular.

Displayed are least-square mean values and standard error.

*Adjusted for age, sex, and first three principal components of ancestry.

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statistical significance. There were no significant associations of the rs17683011 variant with other measures of LV structure or function among either race group. Taken together, these findings suggest that mechanistically, a functionally modifying variant of SGLT1 may be associated with favourable LV systolic function, and thus lower likelihood of subclinical HF at middle age.

The cardiovascular impact of SGLT1 inhibition is unclear, and variants of SLC5A1 may provide insight. The rs17683011 variant of SLC5A1 results in an amino acid substitution (p.Asn51Ser), has been associated with elevated GLP-1 levels,9 and carries a reduced risk of impaired glucose tolerance.10 These investigations suggest that the rs17683011 variant is functionally modifying; further data are required to understand if this variant results in loss-of-function of SGLT1.9 To our knowledge, the association of this genetic variant with cardiac structure and function has not been described in any population. The current investigation suggests a potential cardiovascular benefit of SGLT1 inhibition, as genetic SGLT1 variation may have long-term salutatory effects upon LV systolic function. The magnitude of difference in GLS among those with and without the variant (1.8% in Black participants) carries clinical implications, as a 1% difference in LV GLS is significantly associated with reduced incidence of HF.15

The rs17683011 variant was significantly associated with better GLS in Black participants. However, the effect size was lower in White participants and did not reach statistical significance. A prior study of this genetic variant also suggests differential associations by race. While the rs17683011 variant was significantly associated with reduced odds of impaired glucose tolerance in the Atherosclerosis Risk in the Communities study, the effect size of this variant in Black participants was substantially greater (OR = 0.39) compared with White participants (OR = 0.73).10 Similarly, in our study, although White participants with rs17683011 had numeri-
cally better GLS than those without it, the effect size was larger and statistically significant in Black participants. The sample size of our study limits power to detect a smaller effect size in White participants. Larger sample sizes are necessary to better understand associations of genetic variation in SGLT1 with cardiac function. Varying linkage disequilibrium patterns and environmental factors may account for the race differences in the genetic associations in our study, and further investigation is required to better understand potential gene–gene or gene–environment interactions to explain these findings.

There are multiple possible explanations behind the isolated association of the rs17683011 variant with GLS as opposed to other measures of cardiac structure and function. First, GLS is an extremely sensitive measure of overall myocardial health and changes to GLS precede changes to other measures of LV systolic function, including circumferential strain and ejection fraction. Second, GLS is specifically reflective of endocardial function, which may be influenced by coronary microvascular function. Given the strong relationship between diabetes and coronary microvascular dysfunction, it is possible that genetic SGLT1 variation leads to favourable coronary microvascular function, which may be important for endocardial LV systolic function (reflected by GLS). Third, CARDIA is a relatively young and healthy cohort, and thus, marked abnormalities in cardiac mechanics are not expected.

Further investigation is required to understand possible mechanisms behind the association of genetic variation in SGLT1 with favourable LV GLS. As SGLT1 is highly expressed on cardiomyocytes and higher LV myocardial SGLT1 expression is associated with more advanced cardiac remodelling and reduced systolic function, further investigation is required to understand if genetic variation in SGLT1 leads to improved LV systolic function through direct cardiac effects (as opposed to mediation through improved glucose tolerance). The incremental benefit of SGLT1 inhibition in the setting of SGLT2 inhibition requires further understanding, as genetic variation in SGLT2 is also associated with reduced HF risk. Finally, the association of genetic variation of SGLT1 with cardiac structure and function in populations with prevalent cardiometabolic disease (diabetes and heart failure) require further understanding.

Our study has limitations. Our sample size may have limited power to detect other differences in clinical characteristics or cardiac structure and function by rs17683011 carrier status. Thus, our findings are exploratory and require validation in larger, ethnically diverse populations. We could not evaluate the association of genetic variation in SGLT1 with incident HF because of the low frequency of events given the age of the CARDIA population. Serum GLP-1 levels were not available in the CARDIA cohort, which prevented validation of associations of rs17683011 with GLP-1 levels after glucose tolerance testing. However, prior GWAS have identified and validated such associations.

The rs17683011 variant, a functionally modifying variant of the SGLT1 gene, is associated with more favourable GLS at middle-age. These findings suggest the hypothesis that SGLT1 inhibition might provide protection from subclinical LV systolic dysfunction. Further investigation is warranted regarding the association of functionally modifying variants of SGLT1 with incident HF and its subtypes and the potential role of SGLT1 inhibition for HF prevention.

Conflict of interest

Dr. Muthiah Vaduganathan has received research grant support or served on advisory boards for American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Cytokinetics, Lexicon Pharmaceuticals, Relypsa, and Roche Diagnostics, speaker engagements with Novartis and Roche Diagnostics, and participates on clinical endpoint committees for studies sponsored by Galmed and Novartis. Dr. Sanjiv Shah has received research grants from Actelion, AstraZeneca, Corvia, and Novartis, and consulting fees from Actelion, Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, Cardioria, Eisai, Ironwood, Merck, MyoKardia, Novartis, Sanofi, and United Therapeutics. The remaining authors have nothing to disclose.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supporting information
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