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**Differential Association of Genetic Risk of Coronary Artery Disease with Development of Heart Failure with Reduced Versus Preserved Ejection Fraction: A GoDARTS Mendelian Randomization Study and Meta-Analysis**

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The data that support the findings of this study are available from the corresponding author upon reasonable request.

While there is a broad consensus that coronary artery disease (CAD) contributes to the development of HF with reduced ejection fraction (HFrEF), its causal role in HF with preserved ejection fraction (HFpEF) is less clear. Conventional observational studies reporting the link between CAD and HFpEF are limited by confounding. Use of genetic risk scores (GRS) comprising genetic variants robustly associated with a particular phenotype from genome-wide association studies (GWAS) can largely overcome confounding through independent causal association of the GRS with the clinical outcome using Mendelian randomisation. A recent study from the Framingham cohort suggested that a CAD GRS of 58 genetic variants was associated with HFrEF, but not HFpEF, however this study was underpowered to draw definitive conclusions and did not account for competing risks.[1] The aim of our study was to investigate further the differential association of CAD with incident HFrEF and HFpEF in a large, adequately powered population study and meta-analysis.

We conducted a longitudinal analysis of the Genetics of Diabetes Audit and Research Tayside Scotland (GoDARTS) study.[2] All patients provided informed consent and the study was approved by the East of Scotland Research and Ethics Committee. The primary outcome was time to development of HFrEF or HFpEF. HF mortality and hospitalisation were obtained from electronic health records including any clinically-requested echocardiograms.[3] HFrEF was classified as HF mortality or hospitalisation with LVEF <50%, while HFpEF was classed as HF with LVEF ≥50%. The CAD GRS was constructed based on 64 variants significantly associated with CAD in a 2015 GWAS.[4] Weighting was applied to the SNPs according to the beta estimates reported in the study and an additive risk score was calculated for each patient based on the number of risk alleles and their weighting. Both observational CAD (history of MI prior to study entry) and genetically-determined CAD (CAD GRS) were analysed for association with incident HFrEF and HFpEF with death and the other HF phenotype treated as competing risks using the Fine-Gray method. Hazard ratios for development of HF were calculated with adjustment for age, gender, smoking, diabetes, systolic blood pressure, total cholesterol and HDL cholesterol. Finally, fixed-effects meta-analysis was performed combining our results with those of Andersson et al.[1] A key issue of

Mendelian randomization studies is ensuring adequate statistical power. A post-hoc power calculation was performed using the methods described by Burgess et al.[5] Our meta-analysis had 99.9% power to detect an association between CAD GRS and HFrEF and 91.7% power for the detection of a significant association between the CAD GRS and HFpEF. A p value <0.05 was considered significant. Statistical analyses were performed using R version 3.4.3 and RevMan version 5.3.

12,919 individuals with available genetic data were included in this study (mean age 63±12 years; 54.3% male). 64.5% had diabetes, 8.9% prior myocardial infarction (MI) or unstable angina and 2.7% prior history of HF. There were 1,293 HF events, including 752 HFrEF and 442 HFpEF events. 99 HF events were unclassified (no echocardiography available).

Of the 1,152 patients with prior MI, 220 patients developed HFrEF while 95 patients developed HFpEF. Prior MI was significantly associated with both HF phenotypes (HFrEF: HR 2.84; 95% CI 2.39-3.37; HFpEF: HR 2.25: 95% CI 1.78-2.84; all p<0.00001). Conversely, the CAD GRS was only significantly associated with HFrEF (fully adjusted HR 1.33 per 1-unit increase in GRS; 95% CI 1.09-1.62, p=0.001) but not HFpEF (fully adjusted HR 1.07 per 1-unit increase in GRS; 95% CI 0.83-1.37, p=0.46) **(Figure Panel A)**. Our meta-analysis included 17,309 individuals, with 964 HFrEF events and 638 HFpEF events. After adjustment the CAD GRS was significantly associated with HFrEF (HR 1.43 per 1-unit increase in GRS; 95% CI 1.20-1.69, p<0.0001). Conversely the CAD GRS was not associated with HFpEF (fully adjusted HR 1.06 per 1-unit increase in GRS; 95% CI 0.86-1.30, p=0.52) **(Figure Panel B)**.

Our key finding is that while there is an observational association of CAD with both HFpEF and HFrEF, using Mendelian randomization we found that genetically-determined risk of CAD is significantly associated with HFrEF but not HFpEF. We have combined our study with a previous study[1] in a meta-analysis to provide further confidence for this finding. Overall this analysis strongly supports the conclusion that CAD may not be causal in HFpEF and its high prevalence in patients with HFpEF is likely to be through other commonly associated risk factors.

Our study has some limitations. We used a pragmatic approach to classify patients with HFpEF, and did not have measures such as natriuretic peptides and left atrial size. Secondly, although we had adequate power to determine an effect of the CAD GRS on development of HFpEF, it is possible that a larger population might detect a smaller but significant effect, although the clinical importance of this would be unclear.

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**FIGURE LEGEND**

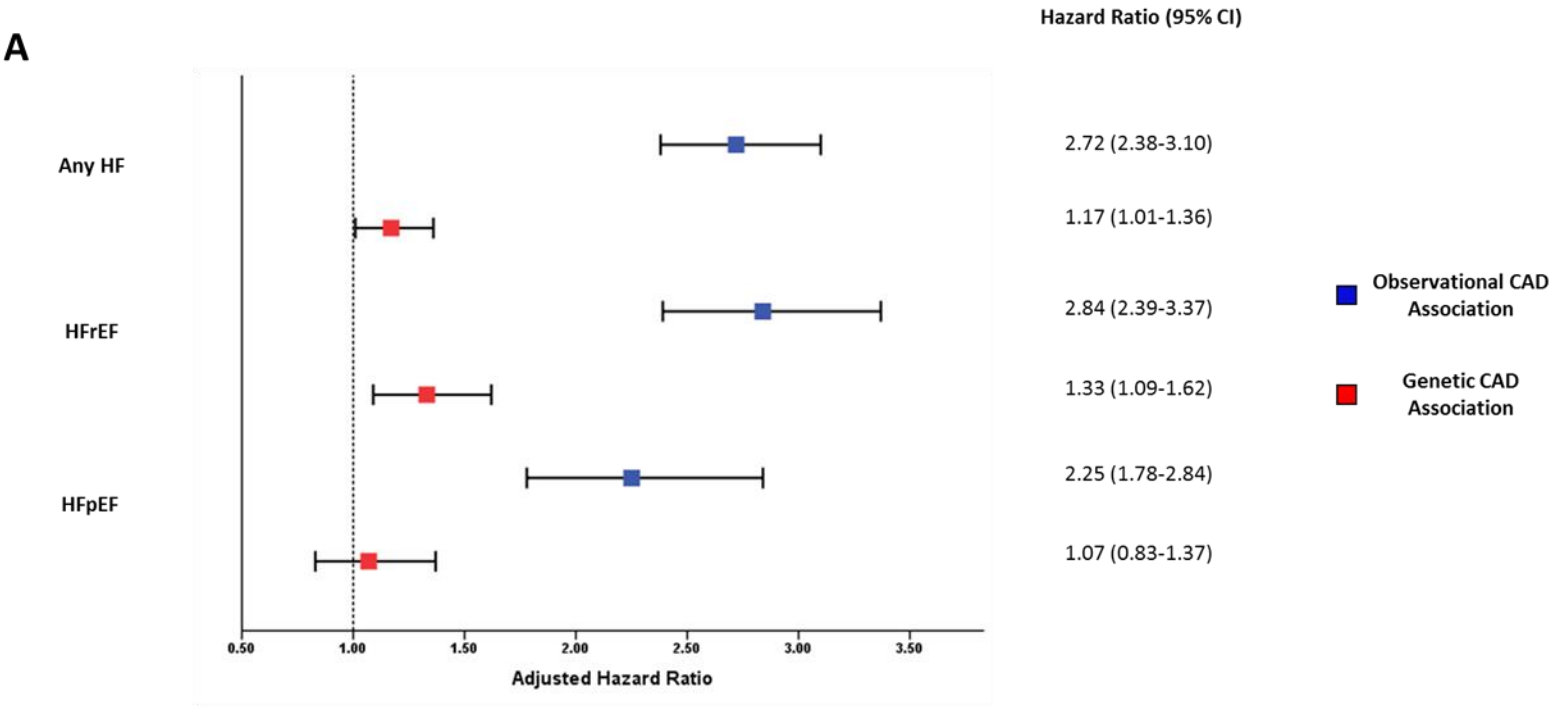
Association of Coronary Artery Disease with Risk of Heart Failure with Reduced versus Preserved Ejection Fraction.

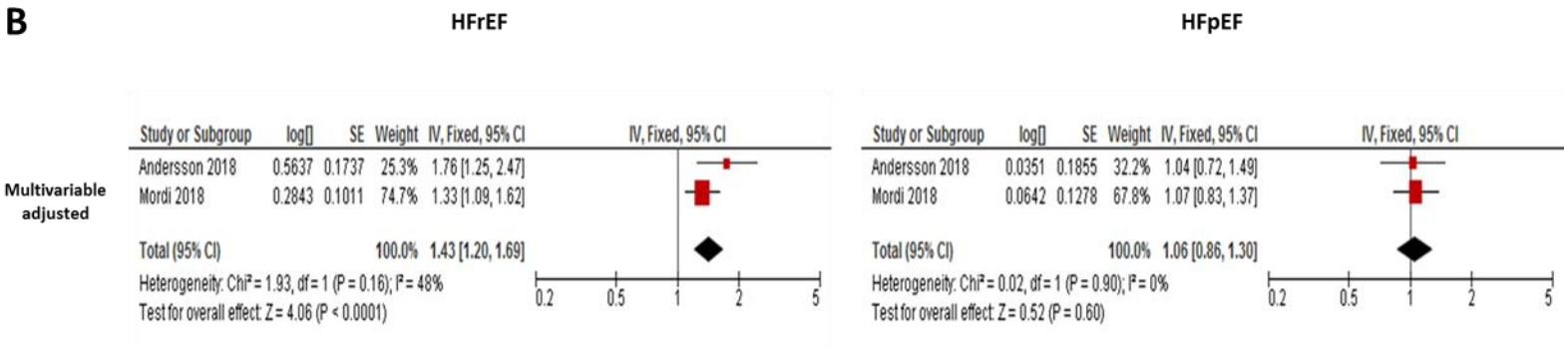
A. Adjusted Hazard Ratios for Observational (red) and Genetic (blue) CAD Risk for Incidence of HF.

   Comparison of fully adjusted hazard ratios for observational and genetic CAD risk for risk of HF. Dotted line represents hazard ratio = 1. Hazard Ratios adjusted for age, gender, smoking, diabetes, systolic blood pressure, total cholesterol and HDL cholesterol.

B. Meta-analysis of CAD GRS for risk of HF.

   Fixed-effects meta-analysis of studies by Andersson et al.[1] and the current study for association of CAD GRS with HFrEF and HFpEF.


A
Hazard Ratio (95% CI)
Any HF
HFrEF
HFpEF
2.72 (2.38-3.10)
1.17 (1.01-1.36)
2.84 (2.39-3.37)
1.33 (1.09-1.62)
2.25 (1.78-2.84)
1.07 (0.83-1.37)
Observational CAD Association
Genetic CAD Association
0.50
1.00
1.50
2.00
2.50
3.00
3.50
Adjusted Hazard Ratio


B
HFrEF
HFpEF
Multivariable adjusted
Study or Subgroup log[] SE Weight IV, Fixed, 95% CI
Andersson 2018 0.5637 0.1737 25.3% 1.76 [1.25, 2.47]
Mordi 2018 0.2843 0.1011 74.7% 1.33 [1.09, 1.62]
Total (95% CI) 100.0% 1.43 [1.20, 1.69]
Heterogeneity: Chi² = 1.93, df = 1 (P = 0.16); I² = 48%
Test for overall effect: Z = 4.06 (P < 0.0001)
IV, Fixed, 95% CI
0.2
0.5
1
2
5
Study or Subgroup log[] SE Weight IV, Fixed, 95% CI
Andersson 2018 0.0351 0.1855 32.2% 1.04 [0.72, 1.49]
Mordi 2018 0.0642 0.1278 67.8% 1.07 [0.83, 1.37]
Total (95% CI) 100.0% 1.06 [0.86, 1.30]
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.90); I² = 0%
Test for overall effect: Z = 0.52 (P = 0.60)
IV, Fixed, 95% CI
0.2
0.5
1
2
5