# Association Between Family History, a Genetic Risk Score, and Severity of Coronary Artery Disease in Patients With Premature Acute Coronary Syndromes

Waseem Hindieh, Louise Pilote, Asim Cheema, Hatim Al-Lawati, Christopher Labos, Line Dufresne, James C. Engert, George Thanassoulis, for the PRAXY Investigators*

***Objective***—A genetic risk score (GRS) for coronary artery disease has recently been shown to be independent of family history (FHx) in predicting future cardiovascular events. We sought to determine whether the presence of these risk factors, either individually or together, was associated with a higher burden of angiographic coronary artery disease.

***Approach and Results***—We included 763 patients with premature acute coronary syndrome (median age, 50 [46–53] years; 30.8% women) with at least 1 major epicardial vessel stenosis enrolled in the Gender and Sex Determinants of Cardiovascular Disease From Bench to Beyond in Premature Acute Coronary Syndrome (GENESIS-PRAXY) study, a multicentre prospective cohort study of premature patients with acute coronary syndrome (aged ≤55 years). The prevalence of multivessel disease (ie, ≥2 vessels with >50% stenosis) in individuals with FHx was 49.7% as compared with 37.9% in those without FHx ($P<0.01$ for comparison). In adjusted models for age, sex, traditional risk factors, and GRS, FHx was associated with a higher prevalence of 3-vessel disease (odds ratio [OR], 1.42; 95% confidence interval, 0.91–2.21; $P=0.12$ for 2-vessel disease and OR, 2.26; 95% confidence interval, 1.29–3.95; $P=0.005$ for 3-vessel disease). Individuals with a high GRS were also more likely to have multivessel disease (OR, 1.41; 95% confidence interval, 1.01–1.99; $P=0.047$) after adjustment for traditional risk factors, including FHx. Individuals with both a FHx and a high GRS as compared with those with neither had the highest ORs for multivessel disease (adjusted OR, 2.14; 95% confidence interval, 1.24–3.69; $P=0.0064$).

***Conclusions***—In patients with premature acute coronary syndrome, the presence of either a high GRS or FHx is associated with greater severity of coronary artery disease at angiography. Whether preventive strategies targeted to genetically predisposed individuals will reduce the burden of early acute coronary syndrome warrants further study. **(*Arterioscler Thromb Vasc Biol*. 2016;36:1286-1292. DOI: 10.1161/ATVBAHA.115.306944.)**

**Key Words:** acute coronary syndrome ■ atherosclerosis ■ cohort studies ■ coronary heart disease ■ genetics ■ myocardial infarction

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The familial clustering of coronary artery disease (CAD) is well documented and likely results from a confluence of environmental factors, heritability of conventional risk factors, and specific predisposing genetic mechanisms.[1–3] Several studies have shown that family history (FHx) of CAD is strongly associated with incident cardiovascular disease, independent of traditional risk factors, and improves risk assessment.[4–8] Recently, genetic risk scores (GRSs) for CAD, consisting of specific genetic variants identified from genome-wide association studies, have also been associated with incident cardiovascular disease and have shown promise in improving cardiovascular risk prediction.[9–22] However, the exact predisposing mechanisms that account for the increased risk in patients with a FHx or a high GRS remain unclear.

A positive FHx and a high GRS may predispose to acute coronary syndrome (ACS) via accelerated atherosclerosis, a propensity to thrombosis or other, as of yet, undetermined mechanisms. Both a FHx and a GRS have been previously shown to associate with subclinical atherosclerosis and most recently have been shown to each provide independent information for future cardiovascular events that seems additive when both are present.[23] Whether this association may be mediated by more advanced angiographic burden of CAD, as opposed to a higher propensity for thrombosis or other mechanism, has not been established.[11,24–27] Accordingly, we evaluated whether a FHx of premature myocardial infarction (MI) and a GRS comprised of 30 single-nucleotide polymorphisms (SNPs) identified in genome-wide association studies were independently associated with the burden of CAD at the time of angiography in young patients (aged ≤55 years) with ACS and whether the presence of both of these risk factors further increased the extent and severity of angiographic CAD.

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From the Department of Medicine, McGill University, Montreal, Québec, Canada (W.H., L.P., C.L., J.C.E., G.T.); Department of Medicine, University of Toronto, Toronto, Ontario, Canada (A.C., H.A.-L.); and McGill University Health Center Research Institute, Montreal, QC, Canada (L.D., J.C.E.).

*A list of all PRAXY investigators is given in Appendix I and II in the online-only Data Supplement.

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Correspondence to George Thanassoulis, MD, MSc, Preventive and Genomic Cardiology, McGill University Health Center, 1001 Decarie Blvd, D5-1520, Montreal, Québec, H3A 1A1, Canada. E-mail George.thanassoulis@mcgill.ca

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**Nonstandard Abbreviations and Acronyms**

| | |
|---|---|
| **ACS** | acute coronary syndrome |
| **CAD** | coronary artery disease |
| **CCTA** | coronary computed tomographic angiography |
| **CI** | confidence interval |
| **FHx** | family history |
| **FRS** | Framingham risk score |
| **GRS** | genetic risk score |
| **MI** | myocardial infarction |
| **OR** | odds ratio |
| **SNP** | single-nucleotide polymorphism |

## Materials and Methods

Materials and Methods are available in the online-only Data supplement.

## Results

### Baseline Characteristics

The median age of included participants was 50 (interquartile range, 46–53) years, and 30.8% were women. The median GRS was 2.69. Patients with a FHx were younger and had a lower Framingham risk score (FRS) but a higher prevalence of diabetes mellitus, hyperlipidemia, and hypertension. Interestingly, there was a higher prevalence of women with a FHx (Table 1). However, none of these differences reached statistical significance.

### FHx and Angiographic CAD

The majority of patients (59.4%) had single-vessel disease at presentation. The prevalence of multivessel disease (ie, ≥2 vessels with >50% stenosis) in individuals with FHx was 49.7% when compared with 37.9% in those without FHx ($P<0.01$ for comparison). Compared with patients without FHx, patients with a FHx had higher adjusted odds of 3-vessel disease (Table 2). In adjusted analyses, a FHx was associated with multivessel disease (odds ratio [OR], 1.61; 95% confidence interval [CI], 1.09–2.39; $P=0.017$; Table 3).

Age at presentation, hypertension, diabetes mellitus, and smoking were all predictors of multivessel CAD (all $P\leq0.05$; Table 3).

Using a proportional odds model, FHx was significantly associated with a higher number of coronary arteries involved, which persisted after adjustment for traditional risk factors (adjusted OR, 1.72; 95% CI, 1.19–2.45; $P=0.001$). The FRS was also strongly associated with multivessel CAD (OR per FRS point increment, 1.05; 95% CI, 1.03–1.08; $P=0.013$). Stratified analyses by low, intermediate, and high FRS demonstrated the same trend between a higher prevalence of FHx and a greater number of vessels involved (Figure 1).

In sensitivity analyses using FHx of MI at any age in a first-degree relative (rather than a FHx of premature MI), the association between FHx and the number of coronary arteries involved persisted (OR, 1.63; 95% CI, 1.23–2.16; $P<0.001$). Adjustment for traditional risk factors and GRS demonstrated similar results (OR, 1.68; 95% CI, 1.21–2.33; $P=0.0018$). Additional adjustments for continuous systolic blood pressure and low-density lipoprotein cholesterol at presentation for all reported analyses did not materially change these results, and FHx remained significantly associated with burden of angiographic CAD (Table I in the online-only Data Supplement).

### GRS and Angiographic CAD

After adjustment for risk factors, including FHx, a high GRS (defined as more than median GRS) was associated with multivessel disease (OR, 1.41; 95% CI, 1.01–1.99; $P=0.047$) (Table 3). We observed a stronger association between a high GRS and 2-vessel disease than with 3-vessel disease (Table 4).

Stratified analyses by FRS demonstrated higher prevalence of multivessel disease among those with a positive FHx across all categories of FRS, whereas there was a higher prevalence of multivessel disease among those with a high GRS

**Table 1. Patient Characteristics**

| | All Patients (n=776) | FHx⁻ (n=597) | FHx⁺ (n=179) | *P* Value |
|---|---|---|---|---|
| Median age, y (IQR) | 50 (46–53) | 50 (46–53) | 49 (45.5–52) | 0.16 |
| Women, n (%) | 239 (30.8) | 173 (29.0) | 66 (36.9) | 0.05 |
| Diabetes mellitus, n (%) | 127 (16.4) | 94 (15.7) | 33 (18.4) | 0.42 |
| Hyperlipidemia, n (%) | 437 (56.3) | 327 (54.8) | 110 (61.5) | 0.12 |
| Hypertension, n (%) | 371 (47.8) | 278 (46.6) | 93 (52.0) | 0.23 |
| Current cigarette smoking, n (%) | 331 (42.7) | 257 (43.0) | 74 (41.3) | 0.67 |
| Unstable angina, n (%) | 39 (5.0) | 25 (4.2) | 14 (7.8) | 0.08 |
| STEMI, n (%) | 483 (62.2) | 381 (63.8) | 102 (57.0) | 0.11 |
| Non-STEMI, n (%) | 247 (31.8) | 186 (31.2) | 61 (34.1) | 0.47 |
| Mean FRS (SD) | 15.0 (7.4) | 15.1 (7.3) | 14.5 (7.6) | 0.41 |
| Mean GRS (SD)* | 2.69 (0.30) | 2.69 (0.30) | 2.69 (0.30) | 0.96 |

Data presented as the number of patients with percentages except where otherwise specified. FHx indicates family history; FRS, Framingham risk score; GRS, genetic risk score; IQR, interquartile range; and STEMI, ST-segment–elevation myocardial infarction.

*GRS results among the 620 patients with genetic data.

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**Table 2. Proportions With Major Epicardial Vessel Stenosis by FHx Status and Corresponding ORs**

| No. of Major Epicardial Coronary Artery Vessels Involved | All Patients (n=776), n (%) | FHx⁻ (n=597), n (%) | FHx⁺ (n=179), n (%) | Unadjusted OR (95% CI); *P* Value | Adjusted* OR (95% CI); *P* Value |
|---|---|---|---|---|---|
| 1 | 461 (59.4) | 371 (62.1) | 90 (50.3) | Reference | Reference |
| 2 | 210 (27.1) | 155 (26.0) | 55 (30.7) | 1.46 (1.00–2.15); *P*=0.05 | 1.42 (0.91–2.21); *P*=0.12 |
| 3 | 105 (13.5) | 71 (11.9) | 34 (19.0) | 1.97 (1.23–3.16); *P*=0.004 | 2.26 (1.29–3.95); *P*=0.005 |

CI indicates confidence interval; FHx, family history; and OR, odds ratio.

*Adjusted for age, sex, history of hypercholesterolemia, history of diabetes mellitus, history of hypertension, current cigarette smoking, and genetic risk score.

in the intermediate- and high-risk categories (Figure 1). In exploratory analyses, individual SNPs were not significantly associated with CAD burden (Table II in the online-only Data Supplement). In additional analyses, we found a nonsignificant trend between a continuous GRS and multivessel disease (OR per GRS unit, 1.08; 95% CI, 0.91–1.28; *P*=0.36).

### Joint Associations Between a GRS and FHx With Angiographic CAD

There were no differences in GRS among patients with and without FHx (2.69 versus 2.69 for FHx⁺ and FHx⁻, respectively). Given that FHx and a high GRS seemed to be largely independent, we evaluated the effect of the joint presence of these genetic risk factors on multivessel disease. The prevalence of multivessel disease across FHx and GRS groups was 33.7% (FHx⁻/GRS low), 41.4% (FHx⁻/GRS high), 45.7% (FHx⁺/GRS low), and 51.3% (FHx⁺/GRS high). The proportion trend test *P* value was 0.003. When compared with patients who were FHx⁻/GRS low, the adjusted ORs for multivessel disease were 1.52 (95% CI, 1.02–2.26; *P*=0.04), 1.87 (95% CI, 1.06–3.31; *P*=0.03), and 2.14 (95% CI, 1.24–3.69; *P*=0.006) for FHx⁻/GRS high, FHx⁺/GRS low, and FHx⁺/GRS high, respectively (Figure 2).

## Discussion

In this study of 763 patients with premature ACS, we demonstrate that FHx of premature MI is strongly associated with CAD severity at angiography as quantified by the number of epicardial vessels with >50% stenosis. We observed that a FHx is associated with a nearly 60% higher odds of multivessel disease and a 2× greater likelihood of 3-vessel disease at ACS presentation, independent of traditional risk factors. Furthermore, we show that a high GRS was also associated with multivessel disease at angiography, even after adjustment for traditional risk factors, including FHx. Our results indicate that a genetic predisposition to MI or CAD, measured either as a FHx or a GRS, which are both known to predispose to early subclinical atherosclerosis, culminates in extensive clinically important CAD in young patients with ACS. Our results also demonstrate that the familial association with CAD severity was independent from the GRS, which indicates that common variants are unlikely to mediate the familial association we observed. Whether additional genetic variants, such as rare or private variants, or other unmeasured familial environmental factors, contribute to the familial association with CAD severity will require further study. Nonetheless, our findings suggest that the presence of a high GRS is additive to FHx and the presence of both a high GRS and a FHx is associated with a higher prevalence of multivessel disease in young patients with ACS, a novel finding that, to our knowledge, has not been previously reported. Our results demonstrate the importance of FHx and a GRS as independent markers for accelerated atherosclerosis, each contributing to the severity of CAD in young patients, and highlight the need to identify preventive strategies that will slow the progression of vascular disease in these genetically predisposed individuals.

Although limited data exist regarding the association between FHx and angiographic CAD severity in patients with ACS, several previous studies have investigated the relationship between FHx and burden of subclinical CAD using coronary calcium or coronary computed tomographic angiography (CCTA). Parikh et al[25] demonstrated that a FHx of CAD was associated with increased subclinical coronary disease as measured by coronary artery calcification in the Framingham Offspring Study, which has also been confirmed in the Multi-Ethnic Study of Atherosclerosis.[28] Otaki et al[29] prospectively evaluated a subset of young patients (n=6308, men aged <55 years and women aged <65 years) from the Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter Registry (CONFIRM) who underwent CCTA for suspected CAD. They found that compared with patients without a positive FHx, patients with a positive FHx had a higher prevalence of any CAD (40% versus 30%;

**Table 3. Associations Between Risk Factors and Multivessel Disease in Patients With Premature Acute Coronary Syndrome**

| Covariates | Adjusted OR | 95% CI | | *P* Value |
|---|---|---|---|---|
| High GRS (more than median) | 1.41 | 1.01 | 1.99 | 0.047 |
| FHx | 1.61 | 1.09 | 2.39 | 0.017 |
| Age at admission (per year) | 1.06 | 1.02 | 1.09 | <0.001 |
| Women | 0.79 | 0.54 | 1.16 | 0.23 |
| Diabetes mellitus | 2.03 | 1.28 | 3.22 | 0.003 |
| Hypertension | 1.64 | 1.15 | 2.35 | 0.007 |
| Hypercholesterolemia | 1.34 | 0.93 | 1.92 | 0.11 |
| Cigarette smoking | 1.59 | 1.09 | 2.39 | 0.009 |

Analysis included 611 patients who were genotyped and had complete risk factor data. All covariates were entered simultaneously into the model. CI indicates confidence interval; FHx, family history; GRS, genetic risk score; and OR, odds ratio.

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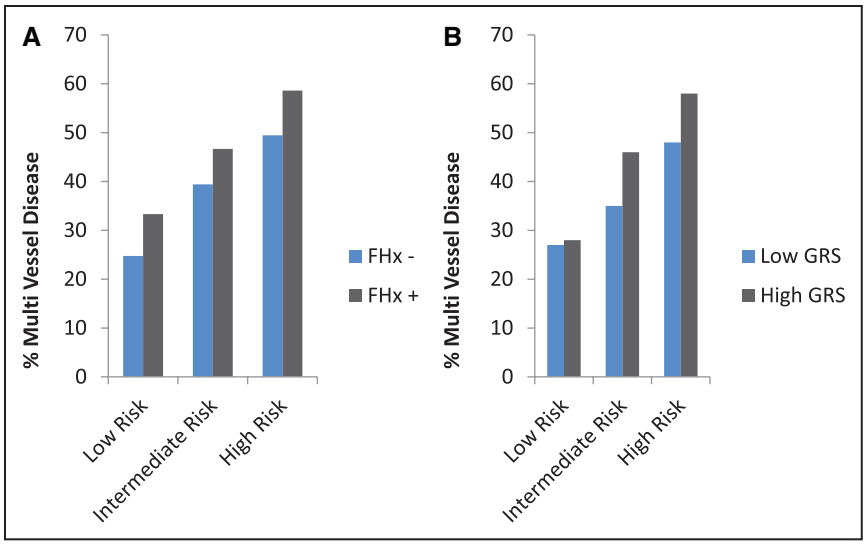


**Figure 1.** Prevalence of multivessel coronary artery disease for family history (FHx; **A**) and high genetic risk score (GRS; **B**) stratified by Framingham risk score categories. Low-, intermediate-, and high-risk correspond to <10%, 10% to 20%, and >20% predicted 10-year risk.

*P*<0.001) and obstructive CAD (11% versus 7%; *P*<0.001) on CCTA. Similarly, Sunman et al[30] investigated patients (n=349; mean age, 57.8±10.8 years) who underwent CCTA for suspected CAD and reported that a positive FHx was associated with a higher presence of CAD, with a predilection for stenosis in left anterior descending (79.8% versus 58.0%; *P*=0.013) and left circumflex arteries (42.3% versus 30.4%; *P*=0.021). These previous studies focused on relatively low-risk individuals with suspected CAD referred for CCTA where the prevalence of multivessel disease was low and therefore could not evaluate the association with disease severity or multivessel disease. Our study, therefore, extends the known relationship between FHx and the presence of CAD on CCTA to younger patients with severe clinically apparent CAD on angiography and indicates that the association with advanced atherosclerosis conferred by FHx persists throughout the spectrum of CAD from early subclinical disease to advanced clinical stenoses.

Previous studies have also looked at associations between CAD/MI-associated SNPs and severity of CAD. Dandona et al[31] established a strong association between 3-vessel disease and 9p21 gene dosage in young nondiabetic patients (n=950; age, 56.1±9.6 years), which was replicated in an older patient cohort (n=764; age, 70.0±8.0 years). A meta-analysis has confirmed that 9p21 risk alleles are associated with a higher prevalence of CAD, demonstrating a weak but statistically significant 10% increase per risk allele for multivessel disease when compared with single-vessel disease.[32] However, we were unable to demonstrate an association with CAD burden among the individual SNPs used in our GRS, including 9p21. In view of the current evidence with respect to 9p21, our inability to establish an association may have been because of the much younger age at the time of angiography, the acute nature of the presentation (ie, ACS rather than stable CAD), or the smaller sample size (to detect the modest association) available for these analyses.

Recently, Bjornsson et al[33] demonstrated that individuals in the upper quintile of GRS had a significantly higher burden of multivessel CAD when compared with the lowest quintile, in a large cohort of Icelandic patients referred for angiography (n=8622; age, 64.4±10.7), which persisted after adjustment for traditional risk factors. The effects of GRS on extent of CAD were found to be independent of FHx of premature CAD. We now extend this association to patients with ACS aged <55 years, showing that even among relatively young patients with an acute ACS, a high GRS is associated with multivessel CAD at presentation and seems to be additive to FHx, which, to our knowledge, has not been previously described. These results are in keeping with recent evidence that the presence of both a FHx and a high GRS leads to a higher risk of cardiovascular events than either alone.[23] Our findings indicate that accelerated atherosclerosis and the presence of more advanced CAD (rather than thrombosis) may mediate the higher cardiovascular risk in individuals with both a FHx and a high GRS. We, and others, have previously shown that a GRS predisposes to accelerated coronary calcium,[11] incident

**Table 4. Proportions With Major Epicardial Vessel Stenosis by High GRS and Corresponding OR**

| No. of Major Epicardial Coronary Artery Vessels Involved | All Patients, n (%) | Low GRS, n (%) | High GRS, n (%) | Unadjusted OR (95% CI); *P* Value | Adjusted* OR (95% CI); *P* Value |
|---|---|---|---|---|---|
| 1 | 371 (59.8) | 201 (62.8) | 170 (56.7) | Reference | Reference |
| 2 | 173 (27.9) | 79 (24.7) | 94 (31.3) | 1.41 (0.98–2.02); *P*=0.065 | 1.51 (1.03–2.21); *P*=0.033 |
| 3 | 76 (12.3) | 40 (12.5) | 36 (12.0) | 1.06 (0.65–1.74); *P*=0.81 | 1.40 (0.82–2.37); *P*=0.21 |

CI indicates confidence interval; GRS, genetic risk score; and OR, odds ratio.

*Adjusted for age, sex, history of hypercholesterolemia, history of diabetes mellitus, history of hypertension, current cigarette smoking, and family history.

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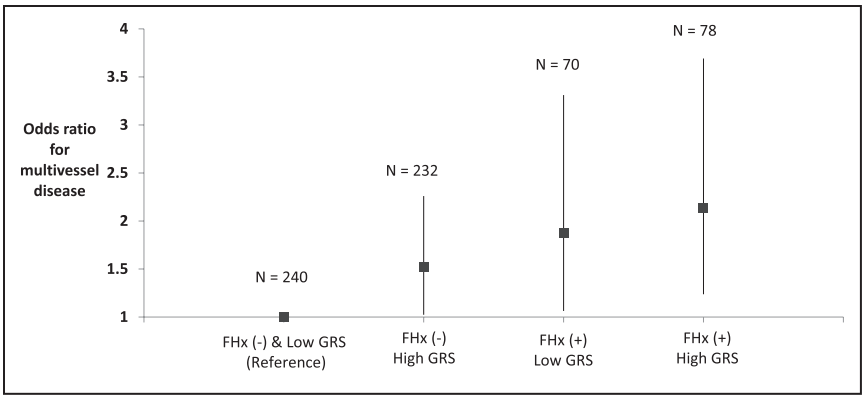


**Figure 2.** Adjusted odds ratios for multivessel disease by family history (FHx) and high genetic risk score (GRS).

cardiovascular events,[9,11,18] and earlier age of first ACS.[34] Therefore, a high GRS seems to contribute to both earlier ACS onset and more extensive CAD at the time of ACS presentation. Our results, therefore, confirm the importance of a high GRS even in individuals with a FHx and demonstrate that each of these factors brings added information in the association with CAD severity.

Our findings raise important issues relevant to clinicians in the care of individuals with a genetic predisposition to CAD. Individuals with a genetic predisposition are known to have a high cardiovascular event rate of similar magnitude to that seen in diabetes mellitus, a CAD equivalent.[35] Although the exact mechanisms for the accelerated CAD remain unknown, poorly controlled risk factors acting in concert with a genetic predisposition to atherosclerosis likely contribute to this observation. Despite the evidence from lifetime risk estimates[36] and Mendelian randomization studies[37,38] stressing the importance of risk factor control early in life, many young genetically predisposed individuals have a high prevalence of poorly controlled risk factors and are frequently missed as candidates for cardiovascular prevention because of low 10-year risk estimates.[39–41] A recent report suggests that individuals with a high GRS derive greater relative risk reductions from statin therapy than those with a low GRS.[42] Therefore, given the rapid progression of atherosclerosis seen in young patients with a high GRS (especially in those who also have a FHx), the overall clinical benefit of initiating statins in young genetically predisposed individuals may be favorable. Whether efforts to screen and implement aggressive risk factor control with lifestyle measures, as well as statins, in all young individuals with a FHx and a high GRS, given their propensity for accelerated atherosclerosis, will lead to reductions in event rates in this vulnerable high-risk population warrants further evaluation in a randomized trial.[43]

Our study has several strengths, including a sizeable sample of premature ACS patients (≤55 years) with complete angiographic data. However, several limitations deserve mention. First, our analysis was a cross-sectional assessment of young patients with ACS; prospective studies evaluating FHx and disease severity are needed to confirm these findings. However, given the low rates of ACS and invasive angiography in young patients, such prospective analyses are frequently limited in this patient population. Hospital-based cross-sectional studies, such as ours, may, therefore, represent a unique approach to address these questions. Second, FHx data were obtained by self-report, which raises the possibility of misclassification bias. However, this would tend to bias our results toward the null. Third, only 30 common MI/CAD-associated SNPs were available in our study. Whether additional SNPs would have strengthened the association between GRS and disease severity remains unclear; however, in previous studies, we have found that the addition of these newly discovered SNPs does not lead to marked improvements in GRS performance.[11] Fourth, we used angiography to determine CAD severity based on the presence of coronary stenosis of >50%, as performed in previous studies, including a recent GRS study.[33] We acknowledge that angiography is not sensitive in identifying less severe lesions or the presence of atherosclerosis. However, our objective was to examine the associations of genetic markers with the extent of advanced coronary lesions. Fifth, although we adjusted for several risk factors, residual confounding may still bias these associations. However, this does not affect the use of FHx or a GRS as a marker to identify young individuals at risk for accelerated atherosclerosis.

## Conclusions

In patients with premature ACS, a genetic predisposition to CAD, based on either a FHx or a high GRS, is associated with accelerated atherosclerosis that culminates in multivessel disease at a young age. Each of these factors seems to be independent and additive for the presence of advanced CAD, and this may mediate the higher rates of cardiovascular events observed in patients with both a FHx and a high GRS. Whether early screening and aggressive preventive strategies could slow the accelerated atherosclerosis observed in individuals genetically predisposed to CAD warrants further study.

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## Disclosures

Dr Thanassoulis has received speaker's bureau honoraria from Servier Canada and has participated in an advisory board for ISIS pharmaceuticals. The other authors report no conflicts.

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## Highlights

- The presence of either a positive family history or a high genetic risk score predisposes to accelerated atherosclerosis that culminates in multivessel disease in young patients with acute coronary syndrome (≤55 years).
- Having both a positive family history and a high genetic risk score is associated with a higher prevalence of multivessel disease than having either of these factors alone, which suggests that accelerated atherosclerosis rather than thrombosis may explain the higher event rate reported in young patients with acute coronary syndrome.
- Whether individuals at high genetic risk may benefit from earlier preventative interventions to slow the rapid progression of vascular disease merits further study.

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