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Utility of a Genetic Risk Score to Predict Recurrent Cardiovascular Events 1 Year After an Acute Coronary Syndrome: A Pooled Analysis of the RISCA, PRAXY, and TRIUMPH Cohorts

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Abstract

Background—Limited evidence exists regarding the utility of genetic risk scores (GRS) in predicting recurrent cardiovascular events after acute coronary syndrome (ACS). We sought to determine whether a GRS would predict early recurrent cardiovascular events within 1 year of ACS.

Methods & Results—Participants admitted with acute coronary syndromes from the RISCA, PRAXY, and TRIUMPH cohorts, were genotyped for 30 single nucleotide polymorphisms (SNPs) associated with coronary artery disease (CAD) or myocardial infarction (MI) in prior genome wide association studies. A 30 SNP CAD/MI GRS was constructed. The primary endpoint was defined as all-cause mortality, recurrent ACS or cardiac re-hospitalization within 1 year of ACS admission. Results across all cohorts for the 30 SNP CAD/MI GRS were pooled using a random-

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effects model. There were 1040 patients from the RISCA cohort, 691 patients from the PRAXY cohort, and 1772 patients from the TRIUMPH cohort included in the analysis and 389 occurrences of the primary endpoint of recurrent events at 1-year post-ACS. In unadjusted and fully adjusted analyses, a 30 SNP GRS was not significantly associated with recurrent events (HR per allele 0.97 (95%CI 0.91–1.03) for RISCA, HR 0.99 (95%CI 0.93–1.05) for PRAXY, 0.98 (95%CI 0.94–1.02) for TRIUMPH, and 0.98 (95%CI 0.95–1.01) for the pooled analysis). Addition of this GRS to the GRACE risk model did not significantly improve risk prediction.

Conclusion—The 30 MI SNP GRS was not associated with recurrent events 1-year post ACS in pooled analyses across cohorts and did not improve risk discrimination or reclassification indices. Our results suggest that the genetic etiology of early events post-ACS may differ from later events.

Keywords

Genetic risk score; recurrent events; acute coronary syndrome

Introduction

Despite optimal medical therapy, early recurrent cardiovascular (CV) events within the first year of a myocardial infarction (MI) remain common and are associated with significant morbidity and mortality[1]. A family history of premature MI is a risk factor for recurrent CV events, which suggests that genetic factors may play a role[2]. Recent large-scale genetic studies have identified several common genetic variants robustly associated with MI[3–12]; however it remains unknown whether such variants predispose to early recurrent CV events. Although the exact biological mechanisms underlying these genetic associations have not yet been elucidated, some of these variants appear to act via non-traditional pathways of atherothrombosis that may not be affected by contemporary secondary prevention therapy. Genetically-predisposed individuals for acute coronary syndromes (ACS) may, in fact, be at high risk for early recurrent events given that current medical treatment may be ineffective in reducing the genetic risk post-ACS which led to the initial CV event. If a genetic risk score (GRS) can further improve the prediction of risk, this may have therapeutic implications in the management of ACS.

Most studies have looked at the use of single SNPs or a genetic risk score (GRS) to predict prevalent or incident cardiovascular disease.[13–22] To date, genetic research on recurrent events post-ACS has been limited.[23, 24] A recent study by Mega et al. showed a strong association between a high GRS and cardiovascular events in both a primary and secondary prevention setting, but did not specifically address early events post-ACS or assess clinical utility.[25] Accordingly, we sought to determine whether a GRS composed of 30 SNPs associated with MI could predict early recurrent events and improve risk stratification within the first year in patients from three hospital-based ACS cohorts.

Methods

Participants

Participants from the Recurrence and Inflammation in the Acute Coronary Syndromes (RISCA) cohort, the Gender and Sex determinants of cardiovascular disease: From bench to beyond-Premature Acute Coronary Syndrome in men and women (PRAXY) cohorts, and the Translational Research Investigating Underlying disparities in acute Myocardial infarction Patients' Health status (TRIUMPH) were included in this analysis.

The RISCA cohort[26] consists of 1210 consecutive patients recruited from four tertiary and four Canadian community hospitals (seven in Quebec and one in New Brunswick). To be eligible, patients had to have an urgent admission to the hospital with a diagnosis of either acute MI or unstable angina. All basic demographic and clinical data were independently verified for consistency and then systematically assessed by on-site visits. Of the 1210 patients enrolled, 1054 provided consent for genetic testing and 14 patients were excluded because of missing covariates, resulting in a final sample of 1040 patients for analysis. Follow-up occurred at 1 month via outpatient visit and at 1 year via a telephone interview.

The PRAXY study is a prospective multicenter study of patients aged 18–55, recruited from 26 centers across Canada, the United States and Switzerland, admitted to hospital with ACS.[27] Patient data was collected with the use of a self-administered questionnaire supplemented by a medical chart review performed by a research nurse. Follow-up occurred at 1, 6 and 12 months via telephone interviews and repeat questionnaires. There were 1123 individuals with follow-up data available in the GENSIS-PRAXY cohort. Genotyping was performed on 705 individuals of European ancestry. Fourteen patients were excluded because of missing covariates, leaving a final sample of 691 participants.

The TRIUMPH cohort[28] is a large, prospective, observational cohort study of consecutive patients with acute MI presenting to 24 US hospitals. Over that time, 6152 subjects were eligible for recruitment and 4340 consented to participate. Consenting patients had detailed chart abstractions of their medical history and processes of inpatient care, supplemented with a detailed baseline interview. The TRIUMPH genetics cohort consisted of 2979 (69%) subjects. The representativeness of the TRIUMPH genetics cohort (compared to the entire TRIUMPH cohort) has previously been reported[29]. GWAS array data were available on 1974 Caucasians from the TRIUMPH genetic cohort. Centralized follow-up interviews occurred at 1, 6 and 12 months. Follow-up data for determination of the primary endpoint was available for 1772 Caucasian patients.

Outcome and Covariate Definitions

The primary outcome was a composite of all-cause mortality, recurrent ACS, and cardiac re-hospitalization. In the RISCA study, all events were verified on-site with the use of supporting documentation. All outcomes were centrally adjudicated and independently reviewed by two cardiologists. Recurrent ACS included both MI and unstable angina. Myocardial infarction was defined as a history of characteristic chest discomfort or pain with an elevation of creatinine kinase – myocardial band to greater than 1.5 times the upper limit of normal or cardiac troponin levels above the upper limit of normal. A diagnosis of

unstable angina required either one episode of characteristic discomfort or pain at rest or with minimal exertion lasting more than 10 minutes or two episodes lasting more than 5 minutes with negative cardiac biomarkers. To increase specificity, UA patients had to have electrocardiogram changes consisting of ≥0.5 mm ST-segment depression or transient ST-segment elevation or ≥2 mm T-wave inversion in 2 contiguous leads. In PRAXY, an acute coronary syndrome was defined as symptoms of chest discomfort with either electrocardiographic changes suggestive of ischemia (such as ST elevation or depression ≥1 mm, new T wave inversions ≥1 mm, pseudo-normalization of previously inverted T waves, new Q waves, new R>S wave in V1, or new left bundle branch block) or an increase in cardiac enzymes (creatine kinase-MB (CK-MB) >2 times the upper limit of the hospital's normal range or if no CK-MB was available, then total creatine phosphokinase > 2 times the upper limit of the hospital's normal range, or positive troponin I or positive troponin T. In TRIUMPH, MI was diagnosed with contemporary definitions,[30] and all patients had an elevated troponin. In follow-up interviews, all patients were asked to report interval events (eg, procedures, diagnostic tests, hospitalizations, and outpatient visits) since their last study contact. If a patient reported being hospitalized since the previous interview, records of that hospitalization were requested to adjudicate cardiovascular events, including MI, heart failure, or revascularization procedures. Chart abstractions were sent to 2 cardiologists who independently classified the reason for hospitalization. If there was disagreement between the 2 cardiologists, the record was adjudicated by a third senior cardiologist, and if disagreement persisted, up to 5 cardiologists independently reviewed the charts until consensus was obtained. The Social Security Administration Death Master File was queried to determine patients' vital status as of 12/31/2010 (http://www.ntis.gov/products/ssa-dmf.asp) and was available for all patients in this study. Of note, this query was performed prior to new restrictions and expunging of some records from the database.

Covariate definitions were standardized across all cohorts for analysis. In each cohort, patients were defined as having a previous history of cardiovascular disease if they had a history of MI before the index hospitalization, previous angina, previous congestive heart failure, prior stroke, or any admission for a cardiac related condition. Patients were defined as having diabetes if they had a history of diabetes, whether treated with medications or by diet. Similarly, patients were defined as having hypertension or hypercholesterolemia if they had a history of hypertension or hypercholesterolemia documented in their medical record, whether treated or untreated. Current smokers were defined as patients who continued to smoke (>1 cigarette per day) at the time of enrolment or who had quit within the past 30 days. Body mass index (BMI) was calculated using height and weight as measured at time of admission. Medication classes were determined by the medications prescribed at the time of discharge.

Development of the genetic risk score

DNA extraction and genotyping was performed using standard techniques. Details are available in the online appendix The genetic risk score (GRS) was determined *a priori* using genotypes from 30 uncorrelated SNPs ($R^2 < 0.3$) in Hardy-Weinberg equilibrium ($p>0.002$) that were robustly associated and replicated in published genome-wide association studies (GWAS) of MI or coronary artery disease.[3–12] (Supplementary Table 1) As performed in

prior work[31], a score for each individual was calculated as the unweighted sum of each risk allele across all 30 SNPs (i.e., score of 2 for those homozygous for the risk allele, a score of 1 for heterozygotes, and a score of zero for the absence of the risk allele). Missing genotypes (<0.35% of all genotypes) were assumed to be missing at random (i.e., non-informative missingness) and were imputed as two times the risk allele frequency, using the risk allele frequencies from each data set. Thus, every individual could have a genetic risk score ranging from 0 to 60; the actual range observed was 18 to 40.

As part of a secondary analysis, a weighted genetic risk score was developed as the sum of the number of risk alleles at each locus weighted by the natural log odds ratio reported for each SNP in the original GWAS studies.[3–12]

Statistical analyses

Continuous variables were reported as means with standard deviations. Categorical variables were reported as counts with proportions. The association between each GRS and recurrent event was assessed using Cox proportional hazards models. Several Cox regression models were constructed: (1) univariate model with only the GRS; (2) adjusted for age and sex; and (3) a multivariate model adjusted for age, sex, previous cardiovascular disease, hypertension, diabetes, hyperlipidemia, body mass index (BMI), smoking status, and medications prescribed at discharge including aspirin, clopidogrel or another thienopyridine, beta-blockers, statins, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB). Log hazard ratios for each GRS were then pooled across all three study samples using a random effects DerSimonian & Laird model. As a secondary analysis, we divided the GRS into tertiles to assess for the potential for non-linearity or a threshold effect. We also analyzed each SNP individually and pooled the results across all the 3 cohorts.

The predictive value of the GRS was also compared to the GRACE risk score. For the GRACE risk score, the percent risk was calculated using the normogram for 6-month outcomes of death or MI.[32] The goodness-of-fit of the models including the GRACE risk score plus the GRS was evaluated using the likelihood ratio test. The predictive value of the GRS added to the GRACE risk score was evaluated using integrated discrimination improvement (IDI),[33] and continuous net re-classification improvement (cNRI).[34]

Several sensitivity analyses were also performed. We examined the performance of the GRS in: (1) individuals presenting to hospital with their first ACS (excluding all forms of previous cardiovascular disease), (2) individuals ≤55 years old, and (3) individuals presenting with STEMI as their initial ACS presentation. All statistical testing was performed using STATA version 12 (StataCorp, College Station, Texas).

Results

Baseline characteristics

There were 1040 individuals from RISCA available for analysis (mean age 61.8±11.4 years; 24.4% female). Over half (55.5%) had a prior history of cardiovascular disease and 28.5% had a prior revascularization with either CABG or PCI. The vast majority (87.4%) had at

least one traditional cardiac risk factor: hypertension, diabetes, cholesterol, or smoking. The mean GRS for the entire population was 31.5 ±3.4. When divided into tertiles based on GRS, the baseline characteristics of the study population were not significantly different. In the RISCA cohort, there were 82 occurrences of the primary composite endpoint including all-cause mortality, recurrent MI, or cardiac re-hospitalization. However, mortality was almost exclusive cardiac in nature, with only 7.3% of deaths being categorized as non-cardiac. One-year follow-up was complete for all subjects.

There were 691 individuals from PRAXY available for analysis (mean age 48.3 +/− 5.6; 27.8% female). The mean GRS for this sample was 30.0 +/− 3.5. Most (85.1%) had at least one traditional cardiac risk factor while 39.8% had a prior history of cardiovascular disease and 14.6% had a prior history of revascularization. When divided into tertiles based on GRS, the baseline characteristics of the study population were not significantly different. There were 93 occurrences of the primary composite endpoint. One-year follow-up was complete for all subjects.

There were 1772 individuals from TRIUMPH available for analysis (mean age 59.9+/−11.9; 27.4% female). The mean GRS for this sample was 30.7 +/− 3.4. Most (87%) had at least one traditional cardiac risk factor while 62% had a previous history of cardiovascular disease and 26.4% had a prior history of revascularization. When divided into tertiles based on GRS, those with higher GRS were more likely to be younger (Anova p=0.023) and have a prior history of revascularization (Anova p=0.0447). There were 214 occurrences of the primary composite endpoint. One-year follow-up was complete for all subjects. Full details of the baseline characteristics of all study populations can be found in Table 1.

Associations between GRACE score, clinical covariates and recurrent events in RISCA PRAXY, and TRIUMPH cohorts

When the clinical covariates in the multivariate model were examined individually, none were consistently predictive of recurrent events across all three cohorts. Only the GRACE score was predictive of recurrent events in all three cohorts. In the pooled analysis across all 3 cohorts, the well-validated GRACE risk score was significantly associated with recurrent events (HR 1.07 per point increase; 95% confidence interval [CI] 1.05–1.09 p<0.001)

Association between 30 MI SNP GRS and recurrent events in RISCA

In RISCA, we found no significant association between the GRS and recurrent events (HR 0.97 per allele; 95% CI 0.91–1.03). Adjustment for age and sex alone, adjustment with the full multivariate model or adjustment for the GRACE risk score did not materially alter the results (Table 2).

When the GRS was added to the GRACE risk model, the likelihood ratio test was not significant (p=0.44). The IDI (p=0.60), and cNRI (p=0.34) also failed to show any incremental predictive ability when the GRS was added to the GRACE score.

Sensitivity analyses limited to young individuals (≤55 years of age), restricted to individuals presenting with their first ACS as the index event, or individuals presenting with STEMI did

not materially change these results and the GRS was not significantly associated with recurrent events. Neither was the GRS associated with all-cause mortality.

Associations between clinical covariates and 30 SNP GRS with recurrent events in PRAXY

In PRAXY, the unadjusted Cox model for the association between GRS and recurrent events yielded a HR of 0.99 per allele (95%CI: 0.93–1.05). Adjustment for age and sex alone, adjustment with the multivariate model, and adjustment for the GRACE risk score did not materially alter the results (Table 2).

When the GRS was added to the GRACE risk model, the likelihood ratio test was not significant (p=0.69). Similarly, there was no improvement in the IDI (p=0.58) or in the NRI (p=0.67). Sensitivity analysis of individuals presenting with their first ACS, or individuals presenting with STEMI did not change the results.

Associations between clinical covariates and 30 SNP GRS with recurrent events in TRIUMPH

In TRIUMPH, the unadjusted Cox model for the association between GRS and recurrent events yielded a HR of 0.98 per allele (95%CI: 0.94–1.02). Adjustment for age and sex alone, adjustment with the multivariate model, and adjustment for the GRACE risk score did not materially alter the results (Table 2).

When the GRS was added to the GRACE risk model, the likelihood ratio test was not significant (p=0.24). Similarly, there was no improvement in the IDI (p=0.49) or in the NRI (p=0.25). Sensitivity analysis of individuals presenting with their first ACS, or individuals presenting with STEMI did not significantly alter the results.

Pooled association results for the 30 SNP MI GRS with recurrent events

Pooling the results from the multivariable model of the RISCA and PRAXY and TRIUMPH cohorts using the DerSimonian & Laird random effects model did not significantly change the results for the 30-SNP GRS (HR: 0.98; 95%CI: 0.95–1.01). As part of a secondary analysis, the association between a weighted GRS and recurrent events was also examined. The weighted GRS was not associated with recurrent events in RISCA (HR 0.96; 95%CI: 0.86–1.07), PRAXY (HR 0.97; 95%CI: 0.87–1.08), TRIUMPH (HR 0.84; 95%CI: 0.60–1.17), or when pooled across the 3 cohorts (HR 0.96; 95%CI: 0.89–1.03).

Association between individual SNPs and recurrent events in all 3 cohorts

When the 30 SNPs were examined individually, and the results pooled across all 3 cohorts, two SNPs were found to have statistically significant association with recurrent events. (Table 3) Rs10953541 was associated with recurrent events (pooled HR1.22 95%CI 1.03–1.45, p=0.023) whereas rs12190287 was inversely associated with recurrent events (pooled HR 0.80 95%CI 0.68–0.93, p=0.003). However, neither of these associations survived the Bonferonni correction for multiple hypothesis testing (p=0.05/30 =0.002).

Discussion

In our combined analysis of the RISCA, PRAXY, and TRIUMPH cohorts consisting of 3,503 participants admitted with ACS and 389 occurrences of the primary endpoint of recurrent events at 1year post-ACS, a GRS composed of 30 MI SNPs was not predictive of adverse events. Based on our results, we can confidently exclude a large effect of a GRS (upper CI for effect was 1% risk per allele) as a predictor of early recurrent events post-ACS.

Two reports from the GRACE study have examined single SNPs and recurrent events after ACS. Buysschaert et al. identified a single SNP at the 9p21 locus that was associated with the composite outcome of recurrent MI and mortality at 6 months post ACS and that improved reclassification when added to the GRACE score.[23] However, this SNP was not associated with the primary outcome of recurrent MI after multivariable adjustment and three other SNPs at the 9p21 locus showed no association.[23] A recent large-scale meta-analysis has now convincingly demonstrated that 9p21 is not associated with recurrent events in individuals with pre-existing coronary disease.[35] Subsequently, Wauters et al. examined 23 single SNPs and found one SNP, rs579459, upstream of the ABO gene, to be significantly associated with recurrent MI.[24] Although the 23 SNPs were not considered in aggregate as a GRS, the majority of the SNPs analyzed were not predictive of recurrent events, which is consistent with our findings of a lack of association between a composite GRS of 30 SNPs and recurrent events.

Tragante et al.[36] also evaluated a GRS consisting of MI-associated SNPs as a predictor of recurrent events. They reported a weak association between the GRS and MI only, but not with the outcome of all cardiovascular events. Although the GRS was modestly associated with MI in the unadjusted model, it was not statistically significant after multivariable adjustment (HR: 1.13; 95% CI: 1.00–1.28; p=0.071). This analysis was limited to a comparison made between top and bottom quartiles of the GRS rather than considering the entire distribution and there were relatively few recurrent events (31 MI in the upper quartile) for analysis. In contrast, our study looked at the entire distribution of the GRS and included a larger number of recurrent events (389 events total; 82 events in RISCA; 93 events in PRAXY; and 214 events in TRIUMPH) that would have been more likely to identify a true significant association. Importantly, a subsequent analysis of the same patient cohort used by Tagrante et al. showed that the GRS did not improve predictive capacity above and beyond the SMART risk score, in patients with established vascular disease.[37]

Recently, Mega et al.[25] demonstrated an association between a 27 SNP GRS and recurrent cardiovascular events in a secondary prevention population in 2438 participants (13.1% event rate). With a similar sample size to ours, they found a significant association for both intermediate genetic risk (HR 1.65 95%CI 1.19–2.30) and high genetic risk patients (HR 1.81 95%CI 1.22–2.67). These results differ markedly from our own findings but it is important to note that there were a number of differences between our study and that of Mega et al.

Firstly, their study used data from a highly selected patient base recruited for randomized trials whereas our cohorts included more typical patients admitted to hospital with ACS. Second, their GRS was composed of 27 SNPs and divided into quintiles whereas we used 30 SNPs and examined our GRS as a continuous variable, consistent with our prior work.[31] As part of a secondary analysis, we divided the GRS into tertiles. We were unable to show any consistent difference in the survivor function between those with a low, intermediate or high GRS across cohorts. Thirdly, the survival analysis performed by Mega et al. was done in the placebo and low intensity statin arms of the trials. By contrast, the majority of our patients were treated with statins. Thus the degree of medical therapy in our two analyses was markedly different and could also partially explain the difference in results. Replication of the findings of Mega et al, with respect to the effect of statins were not performed in our observational cohorts due to the high statin treatment rates and the lack of randomization which may have led to a high risk of bias; rigorous replication of these findings are awaited from other randomized statin trials. Fourthly, and most importantly, we specifically examined early recurrent events whereas their analysis focused on a much longer period post-ACS.

It is conceivable that the longer follow-up time may serve as a possible explanation, such that early events post-ACS (i.e. in the 1st year) may have a different etiology (e.g. more thrombosis or stent restenosis and more likely to be procedural and/or less genetically-mediated) than later events. Thus, it is possible that a GRS may offer some advantage in predicting long term events that have a different mechanism than events in the first year post-ACS. It is also important to note, that prior studies, including the recent study by Mega et al, did not evaluate the clinical utility of a GRS over and above well-validated ACS risk scores. Our results indicate that after considering the clinical variables in GRACE score, a GRS does not improve risk stratification at 1 year.

The utility of a GRS for the prediction of incident CV events in community based cohorts has recently been shown to improve prediction and reclassification indices suggesting that a GRS may have potential to better risk stratify individuals and improve preventive treatment decisions[38]. Despite the relative importance of a GRS with incident events and the fact that current treatments post-ACS may not modify these genetic risks, our findings indicate that in the post-ACS setting the genetic predisposition leading to the initial event does not appear to remain an important predictor of early recurrent events. This may suggest that current post-ACS treatments in our cohorts were sufficient to compensate for the underlying genetic risk and that further genetic risk stratification using MI-related SNPs may not be clinically useful. Alternatively, it may be possible that certain SNPs associated with incident MI/CAD may be predictive of recurrent events but that these effects may be diluted in a GRS comprised of many other SNPs not associated with recurrent events. However, to date, only a single SNP at the ABO locus has been identified and replicated for recurrent events. In our per SNP analysis, we identified two individual SNPs that were statistically significantly associated with recurrent events. However, neither SNP was significant after the Bonferonni correction for multiple hypothesis testing and therefore may represent false positives. One of these SNPs (rs10953541) has been associated with BCAP29 expression in adipose tissue and COG5 in peripheral blood cells but further mechanistic details regarding this locus are not available.[39] Nonetheless, these results should be considered tentative until replicated by

another cohort. Additional studies examining individual SNPs at these MI/CAD loci and across the genome (e.g. in GWAS studies for recurrent events) in large sample sizes with independent replication will be needed to identify specific SNPs predictive for recurrent events.

This study has several limitations. First, we included a heterogeneous patient population with a broad range of ages at presentation and underlying coronary disease severity. Conceivably, younger individuals may be more likely to have a genetic contribution to their risk of recurrent cardiovascular events than older individuals,[40] and older individuals may have more significant coronary disease with different predictors of recurrent risk. However, we found no statistically significant association with the GRS in younger individuals in RISCA or after restricting to individuals in which the index event was the first ACS. Second, our GRS consisted of SNPs discovered before 2012. Although more recently discovered SNPs were not genotyped in our cohorts, we have previously demonstrated that the inclusion of additional SNPs (that invariably have weaker effects) had little impact on the utility of a GRS for prediction.[31] Third, although we had adequate power to detect modest effects of a GRS, we cannot exclude that a GRS may be weakly associated with recurrent events, but this would unlikely be of clinical utility for risk stratification post-ACS. Fourth, we used a composite end-point of all-cause mortality, recurrent events and cardiac re-hospitalization to maximize power for this analysis, as performed by others.[24] Although it is conceivable that the use of a composite end-point may have attenuated the GRS association with recurrent events (e.g. by including rare non-cardiac causes of death that may not be related to the GRS), this outcome captures the most common recurrent events seen clinically post-ACS that may be biologically related to these SNPs.

In summary, we found that a GRS composed of 30 SNPs was not associated with the primary composite outcome of all-cause mortality, recurrent ACS or cardiac re-hospitalization after an ACS admission and does not improve risk stratification afforded by the GRACE score post-ACS. Our results suggest that the genetic etiology of early events post-ACS may differ from later events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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1. A genetic risk score of 30 MI SNPs is not associated with early recurrent events post MI
2. When added to the GRACE risk score, a genetic score does not improve risk prediction for recurrent events post-ACS
3. No individual SNPs were consistently associated with recurrent events across all 3 cohorts after considering multiple hypothesis testing.

Table 1

Baseline characteristics of patients in RISCA, PRAXY, and TRIUMPH

	RISCA n=1040	PRAXY n=691	TRIUMPH n=1772
Age (yrs), mean (sd)	61.8 (11.4)	48 (5.6)	59.93 (11.9)
Female, n (%)	254 (24.4)	192 (27.8)	485 (27.4)
Previous CVD, n (%)	577 (55.5)	275 (39.8)	1102 (62.2)
Previous revascularization, n (%)	296 (28.5)	101 (14.6)	468 (26.4)
Hypertension, n (%)	525 (50.5)	314 (45.4)	1067 (60.2)
Diabetes, n (%)	204 (19.6)	108 (15.6)	437 (24.7)
Hypercholesterolemia, n (%)	644 (61.9)	380 (55.0)	899 (50.7)
BMI (kg/m^2), mean (sd)	27.2 (4.4)	29.4 (6.3)	29.58 (6.3)
Current smoker, n (%)	313 (30.1)	302 (43.7)	642 (36.2)
Coronary angiogram, n (%)	588 (56.5)	572 (82.8)	1711 (96.6)
Medications at discharge			
ASA, n (%)	952 (91.5)	679 (98.3)	1699 (95.9)
Other antiplatelet, n (%)	431 (41.4)	606 (87.7)	1423 (80.3)
Beta-blocker, n (%)	827 (79.5)	598 (86.5)	1627 (91.8)
Statin, n (%)	806 (77.5)	651 (94.2)	1586 (89.5)
ACE-I or ARB, n (%)	609 (58.6)	688 (99.6)	1302 (73.5)
GRACE risk score, mean (sd)	118.1 (39.2)	87.6 (18.6)	99.5 (28.8)

GRS: genetic risk score, sd: standard deviation, CVD cardiovascular disease, BMI body mass index, ASA acetylsalicylic acid, ACE-I angiotensin converting enzyme inhibitor, ARB angiotensin receptor blocker,

Table 2

Hazard ratios for various Cox proportional hazard models of GRS

	RISCA		PRAXY		TRIUMPH		POOLED	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95 CI**
GRS – unadjusted	0.97	0.91–1.03	0.99	0.93–1.05	0.98	0.94–1.02	0.98	0.95–1.01
GRS – adjusted for age & sex	0.97	0.92–1.04	0.99	0.93–1.05	0.98	0.94–1.02	0.98	0.95–1.01
GRS - multivariate model	0.98	0.92–1.04	0.98	0.92–1.04	0.98	0.94–1.02	0.98	0.95–1.01
GRS adjusted for GRACE score	0.97	0.91–1.04	0.99	0.93–1.05	0.98	0.94–1.02	0.98	0.95–1.01

GRS: genetic risk score, CI: confidence interval