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Incremental value of a genetic risk score for the prediction of new vascular events in patients with clinically manifest vascular disease

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ABSTRACT

Background: Several genetic markers are related to incidence of cardiovascular events. We evaluated whether a genetic risk score (GRS) based on 30 single-nucleotide-polymorphisms associated with coronary artery disease (CAD) can improve prediction of 10-year risk of new cardiovascular events in patients with clinical manifest vascular disease.
Methods: In 5742 patients with symptomatic vascular disease enrolled in the SMART study, we developed Cox regression models based on the SMART Risk Score (SRS) and based on the SRS plus the GRS in all patients, in patients with a history of acute arterial thrombotic events and in patients with a history of more stable atherosclerosis and without CAD. The discriminatory ability was expressed by the c-statistic. Model calibration was evaluated by calibration plots. The incremental value of adding the GRS was assessed by net reclassification index (NRI) and decision curve analysis.
Results: During a median follow-up of 6.5 years (IQR4.0–9.5), the composite outcome of myocardial infarction, stroke, or vascular death occurred in 933 patients. Hazard ratios of GRS ranging from 0.86 to 1.35 were observed. The discriminatory capacity of the SRS for prediction of 10-year risk of cardiovascular events was fairly good (c-statistic 0.70, 95%CI 0.68–0.72), similar to the model based on the SRS plus the GRS. Calibration of the models based on SRS and SRS plus GRS was adequate. No increase in c-statistics, categorical NRIs and decision curves was observed when adding the GRS. The continuous NRI improved only in patients with stable atherosclerosis (0.14, 95%CI 0.03–0.25), increasing further excluding patients with a history of CAD (0.21, 95%CI 0.06–0.36).
Conclusions: In patients with symptomatic vascular disease, a GRS did not improve risk prediction of 10-year risk of cardiovascular events beyond clinical characteristics. The GRS might improve risk prediction of first vascular events in the subgroup of patients with a history of stable atherosclerosis.

1. Introduction

Prediction of the risk for development of cardiovascular disease in individual patients is widely used in clinical practice. As patients are treated according to their absolute risks of developing vascular events, accurate risk prediction is very important. Various risk stratification models are available to determine the individual absolute cardiovascular risk in patients without clinical manifest

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vascular disease [1–4]. In patients with clinical manifest vascular disease there is a wide range of absolute risks for developing new acute vascular events [5]. Recently we developed the SMART Risk Score, based on easy-to-measure patient characteristics and traditional risk factors, for risk prediction of vascular events in patients with clinically manifest vascular disease [6]. Although this risk score predicts new events fairly well, addition of other predictors may further optimize this prediction model.

Genome-wide association studies (GWAS) have identified multiple risk loci associated with the development of coronary artery disease (CAD) [7–10], including rs1122608 at the LDLR gene, rs4977574 at 9p21 and rs11206510 at the PCSK9 gene. These individual single-nucleotide polymorphisms (SNPs) provide valuable insight into the underlying biological pathways, but their effect sizes are typically small and individually contribute little to the heritable risk [11]. Associated risk alleles are therefore increasingly combined into multi-locus genetic risk scores for the purpose of prediction [12–14], showing modest improvements in risk prediction of first cardiovascular events in patients free of prevalent vascular disease [12,15]. Because traditional risk factors of cardiovascular disease are easy to measure and frequently available in clinical practice, it is more meaningful to assess the value of a genetic risk score on top of these traditional risk factors than to assess a genetic risk score separately. In addition, traditional risk factors may change over time due to treatment, whereas a genetic risk score remains constant. In patients with diabetes a relation was found between a genetic risk score and cardiovascular mortality (HR 1.46, 95%CI 1.08–1.96) [16] and in patients with clinical manifest vascular disease there was a relation between a genetic risk score and incident myocardial infarction (HR 1.13, 95%CI 1.00–1.28) [14]. Furthermore, a genetic risk score improved risk prediction for individuals at intermediate cardiovascular risk in a two-stage risk screening [17], suggesting a potential role of a genetic risk score in risk prediction of patients with a high risk of cardiovascular disease.

The aim of the present study was to evaluate whether a genetic risk score improves the SMART Risk Score for the prediction of absolute risk of developing new vascular events in patients with clinically manifest vascular disease.

2. Methods

2.1. Study population

The patients included in this study originated from the Second Manifestations of ARTerial disease (SMART) study. The rationale and design of the SMART study have been described previously [18]. In short, the SMART study is an ongoing single-center prospective cohort study that was designed to establish the presence of additional arterial disease and risk factors for atherosclerosis in patients with manifest vascular diseases or a vascular risk factor. The Ethics Committee of the University Medical Center Utrecht approved the study and all participants gave their written informed consent.

For this study data were used of 6580 patients who were newly referred to the University Medical Center between 1996 and 2012 with established clinical manifest arterial disease (i.e. coronary artery disease (CAD), cerebrovascular disease (CVD), peripheral artery disease (PAD) or abdominal aortic aneurysm (AAA)). Patients were enrolled after a stable situation of their disease was reached. Patients with a terminal malignancy were not included, as well as those dependent in daily activities, insufficiently fluent in Dutch language or referred back to the referring physician immediately after one visit.

Of the 6580 patients included in SMART, DNA for genotyping was available of 5742 patients. A history of CAD was present in 3450 patients, of CVD in 1665, of PAD in 1160 and of AAA in 507. A total of 1040 patients fell into more categories because of the presence of more than one clinical manifestation of vascular disease. CAD was defined as myocardial infarction, angina pectoris or coronary revascularization (coronary bypass surgery or coronary angioplasty). Patients with CVD had experienced a transient ischemic attack, cerebral infarction, cerebral ischemia, amaurosis fugax, retinal infarction or a history of carotid artery surgery. PAD was defined as symptomatic and documented obstruction of distal arteries of the lower extremity or interventions (percutaneous transluminal angioplasty (PTA), bypass or amputation). Patients with AAA had a supra- or infrarenal aneurysm of the aorta (distal aortic anteroposterior diameter $\geq$3 cm, measured with ultrasonography) or a history of AAA surgery.

2.2. Baseline measurements

All patients underwent a standardized extensive vascular screening. Patients received a uniform questionnaire on medical history, current medication, symptoms of cardiovascular disease and presence of cardiovascular risk factors. Furthermore, patients underwent laboratory assessments and non-invasive screening for manifestations of atherosclerotic disease and risk factors. Based on the questionnaire, the time since first diagnosis of clinically manifest atherosclerosis was calculated. If the patients' first vascular event occurred in the preceding year, the duration of disease was rounded down to zero years.

2.3. Follow-up

During follow-up, patients were asked biannually to complete a standardized questionnaire on hospital admissions and outpatient clinic visits. The outcome of interest was occurrence of major cardiovascular events, defined as cardiovascular death, ischemic or hemorrhagic stroke or myocardial infarction (Table 1). If a vascular

Table 1
Study outcomes.

Myocardial infarction	Acute chest pain for at least 20 min with ST-segment elevation (STEMI) Acute chest pain without ST-segment elevation with elevated troponin (NSTEMI) Intervention related myocardial infarction Typical pain, remaining STT changes on ECG, no documented cardiac enzymes development Sudden death:unexpected cardiac death occurring within one hour after onset of symptoms, or within 24 h given convincing circumstantial evidence
Stroke	Relevant clinical features for at least 24 h causing an increase in impairment of at least one grade on the modified Ranking scale, with a new cerebral *infarction* on CT or MRI Relevant clinical features for at least 24 h causing an increase in impairment of at least one grade on the modified Ranking scale, with a new cerebral *hemorrhage* on CT or MRI Relevant clinical features for at least 24 h causing an increase in impairment of at least one grade on the modified Ranking scale, *without a new (hemorrhage) or cerebral infarction* on CT or MRI Hemorrhage demonstrated with CT, MRI or operation
Vascular mortality	Death from stroke, myocardial infarction, congestive heart failure, rupture of abdominal aortic aneurysm and vascular death of other causes
Composite vascular outcome	Composite of myocardial infarction, stroke and vascular mortality