Genetic Risk Score Enhances Coronary Artery Disease Risk Prediction in Individuals With Type 1 Diabetes

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OBJECTIVE
Individuals with type 1 diabetes are at a high lifetime risk of coronary artery disease (CAD), calling for early interventions. This study explores the use of a genetic risk score (GRS) for CAD risk prediction, compares it to established clinical markers, and investigates its performance according to the age and pharmacological treatment.

RESEARCH DESIGN AND METHODS
This study in 3,295 individuals with type 1 diabetes from the Finnish Diabetic Nephropathy Study (467 incident CAD, 14.8 years follow-up) used three risk scores: a GRS, a validated clinical score, and their combined score. Hazard ratios (HR) were calculated with Cox regression, and model performances were compared with the Harrell C-index (C-index).

RESULTS
A HR of 6.7 for CAD was observed between the highest and the lowest 5th percentile of the GRS (P = 1.8 × 10−6). The performance of GRS (C-index = 0.562) was similar to HbA1c (C-index = 0.563, P = 0.96 for difference), HDL (C-index = 0.571, P = 0.6), and total cholesterol (C-index = 0.594, P = 0.1). The GRS was not correlated with the clinical score (r = −0.013, P = 0.5). The combined score outperformed the clinical score (C-index = 0.813 vs. C-index = 0.820, P = 0.003). The GRS performed better in individuals below the median age (38.6 years) compared with those above (C-index = 0.637 vs. C-index = 0.546).

CONCLUSIONS
A GRS identified individuals at high risk of CAD and worked better in younger individuals. GRS was also an independent risk factor for CAD, with a predictive power comparable to that of HbA1c and HDL and total cholesterol, and when incorporated into a clinical model, modestly improved the predictions. The GRS promises early risk stratification in clinical practice by enhancing the prediction of CAD.

Despite advances in insulin therapy, delivery systems, and glucose monitoring (1), a significant number of individuals with type 1 diabetes develop diabetic complications that can substantially reduce their quality of life (2), shorten their life span (3), and impose high health care costs (4). Coronary artery disease (CAD) is...
currently the leading cause of morbidity and mortality in type 1 diabetes. Notably, CAD is more common, occurs 10 to 15 years earlier in life, and the protective effect of women is lost in individuals with type 1 diabetes compared with the population without diabetes (5). Mainly attributed to cardiovascular causes of death, the life expectancy is still ~12 years shorter in individuals with type 1 diabetes than in the general population (3).

The conventional modifiable risk factors for CAD, including poor glycemic control, elevated blood pressure (BP), dyslipidemia, and smoking, are well established to increase CAD risk in type 1 diabetes (6). Improved treatment of these risk factors by statin therapy, BP control, and lifestyle modifications have led to a remarkable decrease in the incidence of CAD during recent decades (7). Nonetheless, individuals with type 1 diabetes continue to have an increased risk of cardiovascular events and death compared with the general population (6).

Several cardiovascular disease (CVD) risk prediction models, such as the Framingham Risk Score (8) or UK Prospective Diabetes Study (UKPDS) Risk Engine model (9), have been developed to improve CVD risk stratification. These models, however, underestimate the predicted risk of CVD events in type 1 diabetes (10). Therefore, prediction models, including the Swedish National Diabetes Register risk equation (11) and the Steno Type 1 Risk Engine (12), have been developed. These models have been derived from large cohorts of individuals with type 1 diabetes and have shown comparable performance regarding CVD risk prediction (12). However, these models are all age dependent, can only be applied after clinical risk factors appear (13), and are thus inadequate to identify high-risk individuals at the very early stage. Therefore, better risk stratification for early identification and intervention is urgently needed for type 1 diabetes.

Genetics is also known to contribute to the development of CAD. To date, 163 genetic variants have been genomewide significantly associated with CAD in the general population (14). Of note, although research on type 1 diabetes-specific CAD risk variants has been scarce, there has been evidence for some variants to increase CAD risk only in individuals with type 1 diabetes (15–17). Notably, CAD risk stratification by genetic risk scores (GRSs) has been shown to discriminate high- and low-risk individuals for CAD in the general population (18–20). In fact, Khera et al. (20) reported a large area under curve (AUC) value (0.81) for a genome-wide polygenic risk score (PRS) in CAD prediction. Moreover, there is evidence from the general population that in those with the highest GRS, lifestyle modification or statin therapy reduce the risk of CAD by ~50% and are more effective when initiated at the early stages of the disease (21,22). Furthermore, recent studies have shown similarities between the genetic architecture of CAD in individuals with and without diabetes, also specifically type 1 diabetes, by observing correlated effect estimates on the known loci in genome-wide association studies (GWAS) (15,16,23).

Therefore, in type 1 diabetes, genetic risk stratification based on GRSs can be applied after clinical risk factors appear and lifestyle modification and intervention is ongoing nationwide multicenter study aiming to identify risk factors for diabetic complications in individuals with type 1 diabetes. A more detailed description of the study has been reported elsewhere (24). In short, the study was launched in 1997, and to date, 5,496 adult individuals with type 1 diabetes have been recruited from ≥80 hospitals and health centers throughout Finland (Supplementary Table 1). Type 1 diabetes was defined by age of onset ≤40 years and insulin treatment initiated ≤1 year from diagnosis. The study protocol was approved by the Helsinki and Uusimaa Hospital District Ethics Committee, and the study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant.

Nonfatal CAD events were identified from the Finnish Care Register for Health Care and deaths, including fatal CAD events, from the Causes of Death Register. CAD events, including myocardial infarction (MI) (International Classification of Diseases [ICD] 8/9 Revisions 410, 412; ICD-10 I21-i23), coronary bypass graft surgery, and coronary angioplasty based on the Nordic Classification of Surgical Procedures (Supplementary Table 2).

A clinical risk score for CAD was calculated based on a validated 5-year CVD risk model in type 1 diabetes (11). The model has eight predictors: diabetes duration, onset age of diabetes, total cholesterol-to-HDL cholesterol ratio, HbA1c, systolic BP, smoking status, macroalbuminuria, and previous CVD (11). Diabetic nephropathy (DN) status was defined by urinary albumin excretion rate (AER) or albumin-to-creatinine ratio (ACR) in two of three timed overnight or 24-h urine collections or in morning spot urine samples for ACR. Normal AER was defined as AER <20 μg/min or <30 mg/24 h, or ACR <2.5 mg/mmol for men and <3.5 mg/mmol for women; microalbuminuria as an AER ≥20 and <200 μg/min or ≥30 and <300 mg/24 h, or ACR ≥2.5 and ≤25 mg/mmol for men and ≥3.5 and ≤35 mg/mmol for women; and macroalbuminuria as AER ≥200 μg/min or ≥300 mg/24 h, or ACR ≥25 for men and ≥35 mg/mmol for women. End-stage renal disease was defined as dialysis or kidney transplantation. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Collaboration (CKD-EPI) formula (25). Individuals were classified into five stages according to the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines (26). LDL cholesterol was calculated with the equation from Sampson et al. (27).

We selected individuals from a recent GWAS on CAD in 4,869 individuals with type 1 diabetes in the FinnDiane cohort (16). We excluded 1,420 individuals with missing clinical data and 154 individuals with a CAD event prior to the baseline. Overall, 3,295 individuals with type 1 diabetes
diabetes were included in this study (467 incident cases) (Supplementary Fig. 1A). Participants were followed until an initial CAD event or death, or otherwise, until the end of the follow-up date 31 December 2015.

**Genetic and Combined Risk Scores**

GWAS genotyping and imputation procedures, as well as GRS calculation, have been described elsewhere (16). In short, genotyping was performed at the University of Virginia with HumanCoreExome Bead arrays 12-1.0, 12-1.1, and 24-1.0 113 (Illumina, San Diego, CA), and genotypes were called with zCall software (28). GWAS imputation was performed with minimac3 software (29) using the 1000 Genomes phase 3 reference panel (Hg37). In this study, we calculated an allelic GRS for the study participants with 156 of the currently known 163 general population CAD risk variants (14) available in our GWAS data (Supplementary Table S3). We defined the GRS for an individual as the mean of the variant dosages weighted by their corresponding natural logarithmic odds ratio (OR) from original studies (16),

$$GRS = \frac{\sum_{i=1}^{156} \ln(OR_i) \times Dosage_i}{156}.$$  

The genetic and clinical risk scores were combined by summing up their contributions weighted by respective survival model Harrell C-indexes—from unadjusted models with standardized scores—which were transformed according to \([C\text{-}index - 0.5] \times 2\) for the weighting of parameters to vary between 0 and 1,

$$Combination\ score = [(C\text{-}index_{\text{GRS}} - 0.5) \times 2] \times GRS$$

$$+ \left[\left(\text{indexClinical score} - 0.5\right) \times 2\right] \times \text{Clinical score}.$$  

Finally, we studied a genome-wide PRS designed by Khera et al. (20) for the general population. We calculated the score with plink (https://www.cog-genomics.org/plink/2.0/) using publicly available score weights for the ~6 million variants, of which 5 million were available in our data (https://cvd.hugeamp.org/).

**Pharmacological Treatment**

To estimate the value of GRS in those with pharmacological treatment, the FinnDiane data were linked to the Finnish Drug Prescription Register data (maintained by the National Social Insurance Institution since 1994), available for 3,241 individuals. From the register, information on purchases of antihypertensive (Anatomical Therapeutic Chemical codes C02, C03, C07-C09) and lipid-lowering drugs (Anatomical Therapeutic Chemical code C10) until the end of 2015 were obtained. First, baseline medication status was defined as any purchase of these drugs 180 days before and after the FinnDiane baseline visit. Moreover, to confirm stable medication status at each medication group, refill adherences for antihypertensive and lipid-lowering drugs were calculated for both drugs separately during the follow-up. The acceptable refill period was set to 180 days between two purchases (at least two prescriptions) of these drugs, and if exceeded, uncovered days were calculated from baseline until the end of follow-up. A similar approach used by other researchers (30) was adopted to define adherence thresholds: ≥0.80 was considered satisfactory, while adherence <0.50 was considered poor. We divided individuals into four subgroups based on the baseline medication status and these refill adherence thresholds (Supplementary Fig. 18): antihypertensive drugs only, lipid-lowering drug only, both antihypertensive and lipid-lowering drugs, and none of these drugs.

### Statistical Analysis

Continuous covariates are described with mean ± SD for normally distributed variables, median with interquartile range (IQR) for nonnormally distributed variables. Differences between the groups were tested with the t-test or Wilcoxon signed rank test for normally and nonnormally distributed variables, respectively. Binary variables are expressed as frequency (%), and differences in distributions were tested with the Pearson $\chi^2$ test or two-tailed Fisher exact test, as appropriate. In addition, the correlation structure between the clinical variables was calculated with Spearman rank correlation. We compared individuals in the top and bottom score distribution percentiles with Cox proportional hazard (PH) regression models adjusted for sex and the calendar year of type 1 diabetes onset, and presented results as hazard ratios (HRs) with 95% CIs. Triglycerides and clinical risk score were log10-transformed in all analyses. Furthermore, Cox PH regression models were built for each clinical variable (i.e., sex, smoking, DN status, calendar year of type 1 diabetes onset, age, systolic BP, diastolic BP, waist-to-height ratio, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and HbA1c) and risk score (i.e., GRS, genome-wide PRS, clinical scores, and combined scores). All studied risk scores and clinical variables were standardized to 0 mean and unit SD. Model performances were compared with the Harrell C-index (31). Statistical significances of the differences were evaluated as suggested by Kang et al. (32). Finally, Cox PH regression models were built with standardized clinical covariates and GRS as separate covariates in one model. Statistical analyses were performed in R statistical software (https://www.r-project.org/).

### Data Resource and Availability

No data are available. The ethical statement and the informed consent do not allow for free data availability.

### RESULTS

#### Cohort Characteristics

The study comprised 3,295 individuals with type 1 diabetes, 51% of whom were men. The mean age was 39.1 ± 11.2 years, and mean duration of diabetes was 22.9 ± 11.7 years at baseline. During a median of 14.8 (IQR 11.6–16.8) follow-up years (43,691 person-years), 467 individuals developed CAD (250 nonfatal MIs, 38 fatal MIs, and 179 coronary revascularizations). The characteristics of the case subjects who developed CAD and the control subjects who did not are shown in Table 1, and distributions of each clinical variable between case subjects and control subjects are plotted in Supplementary Figs. 2 and 3. As could be expected, case subjects were older and had longer duration of diabetes. They had also more often signs of traditional clinical risk factors (i.e., reduced renal function and albuminuria, elevated systolic BP, and worse lipid profile and glycemic control) for CAD than control subjects. Consequently, the previously validated clinical risk score also indicated higher clinical risk for CAD in case subjects than in control subjects (Table 1).
GRS and CAD

The GRS differed significantly between those individuals who did and did not develop CAD \( (P = 7.7 \times 10^{-7}) \), although the mean difference was small (Table 1 and Supplementary Fig. 4). We found a clear difference in CAD risk when we compared individuals within the high and low GRS percentiles. These differences were most pronounced when comparing the extreme ends of the GRS distribution. Individuals in the highest 5th percentile showed a 6.7-fold increased risk of CAD compared with those in the lowest 5th percentile (Supplementary Table 4). The increase in risk was more modest but remained steep for the decile (HR 2.99 [95% CI 1.98, 4.50]), for the quintile (HR 2.21 [95% CI 1.64, 2.98]), and for the 30th percentile (HR 1.76 [95% CI 1.39, 2.24]) group comparisons (Supplementary Table 4). There was also a clear difference in the risk when comparing the top and the bottom percentiles of the clinical and combined risk scores (Supplementary Table 4 and Supplementary Fig. 5). Although combining the clinical and genetic risk scores improved the 30th percentile comparison HR from the clinical risk score alone only slightly, the combination score already outperformed the clinical risk score in the quintile comparisons (HR 75.42 [95% CI 25.80, 220.48] vs. HR 85.48 [95% CI 29.67, 246.26], respectively).

Survival model GRS performance (C-index 0.562 [95% CI 0.535, 0.589]) was comparable to the traditional clinical risk factors HbA1c (C-index 0.563, \( P = 1.0 \)), HDL cholesterol (C-index 0.571, \( P = 0.6 \)), LDL cholesterol (C-index 0.598, \( P = 0.064 \)), and total cholesterol (C-index 0.598, \( P = 0.064 \)).

### Table 1—Baseline clinical characteristics of the case subjects who developed CAD and control subjects who did not during the follow-up

<table>
<thead>
<tr>
<th></th>
<th>Case subjects ( n = 467 )</th>
<th>Control subjects ( n = 2,828 )</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46.8 ± 9.7</td>
<td>37.8 ± 10.9</td>
<td>3.0 \times 10^{-60}</td>
</tr>
<tr>
<td>Male sex</td>
<td>252 (54.0)</td>
<td>1,422 (50.3)</td>
<td>0.2</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>31.5 ± 9.8</td>
<td>21.4 ± 11.4</td>
<td>2.2 \times 10^{-71}</td>
</tr>
<tr>
<td>Age at onset of diabetes (years)</td>
<td>13.5 (8.8–20.9)</td>
<td>14.4 (9.5–22.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>DN status</td>
<td></td>
<td></td>
<td>1.1 \times 10^{-61}</td>
</tr>
<tr>
<td>Normal AER</td>
<td>160 (34.3)</td>
<td>1925 (68.1)</td>
<td>NA</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>66 (14.1)</td>
<td>399 (14.1)</td>
<td>NA</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>155 (33.2)</td>
<td>369 (13.0)</td>
<td>NA</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>86 (18.4)</td>
<td>135 (4.8)</td>
<td>NA</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>71.0 (24.8–99.6)</td>
<td>101.2 (83.5–113.8)</td>
<td>6.6 \times 10^{-55}</td>
</tr>
<tr>
<td>Chronic kidney disease (mL/min/1.73 m²)</td>
<td></td>
<td></td>
<td>1.4 \times 10^{-57}</td>
</tr>
<tr>
<td>1 eGFR &gt;90</td>
<td>164 (35.1)</td>
<td>1,917 (67.8)</td>
<td>NA</td>
</tr>
<tr>
<td>2 eGFR 60–89</td>
<td>116 (24.8)</td>
<td>569 (20.1)</td>
<td>NA</td>
</tr>
<tr>
<td>3 eGFR 30–59</td>
<td>62 (13.3)</td>
<td>136 (4.8)</td>
<td>NA</td>
</tr>
<tr>
<td>4 eGFR 15–29</td>
<td>29 (6.2)</td>
<td>52 (1.8)</td>
<td>NA</td>
</tr>
<tr>
<td>5 eGFR &lt;15</td>
<td>96 (20.6)</td>
<td>154 (5.4)</td>
<td>NA</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>146 ± 20</td>
<td>133 ± 18</td>
<td>6.6 \times 10^{-33}</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>81 ± 10</td>
<td>80 ± 10</td>
<td>0.08</td>
</tr>
<tr>
<td>Waist-to-height ratio</td>
<td>0.52 ± 0.06</td>
<td>0.50 ± 0.06</td>
<td>9.3 \times 10^{-11}</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.28 ± 1.13</td>
<td>4.88 ± 0.93</td>
<td>5.7 \times 10^{-13}</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.25 ± 0.37</td>
<td>1.36 ± 0.39</td>
<td>9.4 \times 10^{-10}</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.39 ± 0.95</td>
<td>3.01 ± 0.86</td>
<td>3.8 \times 10^{-15}</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.23 (0.92–1.79)</td>
<td>0.98 (0.74–1.39)</td>
<td>1.1 \times 10^{-19}</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.7 ± 1.5</td>
<td>8.3 ± 1.4</td>
<td>2.3 \times 10^{-6}</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>70 ± 16</td>
<td>67 ± 16</td>
<td>2.3 \times 10^{-6}</td>
</tr>
<tr>
<td>Current or history of smoking</td>
<td>239 (51.2)</td>
<td>1,293 (45.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>28 (6.0)</td>
<td>42 (1.5)</td>
<td>1.1 \times 10^{-9}</td>
</tr>
<tr>
<td>Deceased until 2015</td>
<td>192 (41.1)</td>
<td>286 (10.1)</td>
<td>5.7 \times 10^{-69}</td>
</tr>
<tr>
<td>GRS</td>
<td>0.0086 ± 0.0032</td>
<td>0.0078 ± 0.0032</td>
<td>7.7 \times 10^{-7}</td>
</tr>
<tr>
<td>Clinical risk score</td>
<td>8.17 (4.58–15.44)</td>
<td>2.16 (0.89–4.88)</td>
<td>5.5 \times 10^{-100}</td>
</tr>
</tbody>
</table>

Data are mean ± SD, median (IQR), or \( n \) (%). NA, not applicable.
0.594, \( P = 0.1 \) (Fig. 1). Furthermore, the GRS significantly outperformed sex (C-index 0.520, \( P = 0.02 \)), while we noticed a nonsignificant improvement from smoking (C-index 0.527, \( P = 0.05 \)) and diastolic BP (C-index 0.529, \( P = 0.1 \)) in survival model risk prediction. However, other clinical variables (i.e., triglycerides [C-index 0.629, \( P = 0.0007 \]), DN status [C-index 0.698, \( P = 5.0 \times 10^{-12} \]), systolic BP [C-index 0.700, \( P = 2.8 \times 10^{-12} \]), age [C-index 0.748, \( P < 1.00 \times 10^{-12} \]), and calendar year of type 1 diabetes onset [C-index 0.770, \( P < 1.00 \times 10^{-12} \)]) significantly outperformed the GRS. Furthermore, the genome-wide PRS did not outperform the allelic GRS based on 156 variants (C-index 0.571 vs. 0.562, \( P = 0.46 \)) (Fig. 1). Thus, the subsequent analyses were performed with the GRS with variant effect similarities previously assessed in type 1 diabetes (16). When we combined the genetic and clinical risk scores into a combination score, we saw a modestly improved risk stratification of the individuals over the clinical risk score (C-index for clinical score 0.813 vs. for combined score 0.820, \( P = 0.003 \)). Of note, when we inspected the performance of a multivariable survival model (sex, smoking, DN status, calendar year of type 1 diabetes onset, age, systolic and diastolic BP, waist-to-height ratio, total and HDL cholesterol, triglycerides, and HbA1c), we noticed a similar trend with respect to GRS addition (C-index 0.829 for multivariable clinical model vs. 0.836 for multivariable clinical model with GRS).

In further analyses, we split individuals according to their median age at baseline into two groups (age <38.6 years and age ≥38.6 years). The performance of GRS was better in the younger age-group (C-index 0.637 [95% CI 0.578, 0.705]) than in the older age-group (C-index 0.546 [95% CI 0.516, 0.577]). In the younger age-group, the GRS outperformed sex, smoking, and waist-to-height ratio and was comparable to most of the clinical risk factors, while only DN status outperformed it (Supplementary Fig. 6A). In contrast, most of the clinical variables outperformed the GRS in the older age-group (Supplementary Fig. 6B).

Finally, a multivariable Cox PH model with all clinical variables found that the strongest predictors were age (HR 1.78 [95% CI 1.56, 2.03]), calendar year of type 1 diabetes onset (HR 0.62 [95% CI 0.54, 0.72]), DN status (HR 1.64 [95% CI 1.49, 1.81]), and GRS (HR 1.31 [95% CI 1.19, 1.44]) (Fig. 2). In addition, HDL cholesterol, systolic BP, and HbA1c reached statistical significance after Bonferroni correction, although with more modest effect sizes. Thus, unlike many important clinical variables, such as waist-to-height ratio and total cholesterol, the GRS attained a highly significant association with incident CAD events when adjusted for clinical risk factors. Although the clinical variables strongly correlated with each other, GRS only weakly correlated with HDL, LDL, and total cholesterol (Supplementary Fig. 7), which may explain the clear association between GRS and CAD events in a strongly adjusted model. Of note, no correlation was observed between GRS and clinical risk score (\( r = -0.013, P = 0.5 \)).

Pharmacological Treatment and CAD

As antihypertensive and lipid-lowering medications are an important part of preventing and treating CAD, we estimated the value of GRS in those who were already medicated at baseline and continuously thereafter. As expected, individuals with none of these drugs (n = 1,258) had a shorter duration of diabetes and a better clinical profile compared with those with antihypertensive drugs only (n = 559) or both antihypertensive and lipid-lowering drugs (n = 282) (Supplementary Table 5). No differences in CAD risk were observed between the top and the bottom quintiles in those who were taking both antihypertensive and lipid-lowering drugs (HR 0.99 [95% CI 0.54, 1.84]). On the contrary, there was a clear difference in CAD risk between the top and the bottom GRS quintiles in those on continuous antihypertensive drug treatment only (HR 2.23 [95% CI 1.24, 3.98]). Notably, the HR between the top and the bottom quintiles was almost fourfold (HR 3.78 [95% CI 1.24, 3.98]) in those with no other clinical variables found that the strongest predictors were age (HR 1.78 [95% CI 1.56, 2.03]), calendar year of type 1 diabetes onset (HR 0.62 [95% CI 0.54, 0.72]), DN status (HR 1.64 [95% CI 1.49, 1.81]), and GRS (HR 1.31 [95% CI 1.19, 1.44]) (Fig. 2). In addition, HDL cholesterol, systolic BP, and HbA1c reached statistical significance after Bonferroni correction, although with more modest effect sizes. Thus, unlike many important clinical variables, such as waist-to-height ratio and total cholesterol, the GRS attained a highly significant association with incident CAD events when adjusted for clinical risk factors. Although the clinical variables strongly correlated with each other, GRS only weakly correlated with HDL, LDL, and total cholesterol (Supplementary Fig. 7), which may explain the clear association between GRS and CAD events in a strongly adjusted model. Of note, no correlation was observed between GRS and clinical risk score (\( r = -0.013, P = 0.5 \)).

CONCLUSIONS

Our findings from a representative cohort of individuals with type 1 diabetes illustrate that a general population GRS, built with 156 established CAD risk variants, successfully identified individuals at high risk for CAD. Notably, the GRS was comparable to the risk imposed by traditional risk factors such as HbA1c, HDL, and total cholesterol. The GRS combined with a validated clinical score for individuals with type 1 diabetes discriminated high- and low-risk individuals with high accuracy and modestly improved CAD risk prediction over the clinical risk score. Furthermore, within a multivariable survival model with several clinical risk variables, the GRS stands out as one of the strongest predictors of CAD events, which may be attributable to the GRS not being strongly correlated with the clinical risk factors. Importantly, the GRS showed
better performance in the younger age-group than in the older age-group, suggesting that the GRS is particularly important for the younger individuals. Moreover, our data also demonstrated that among participants without antihypertensive or lipid-lowering medication (mean age 33.6 years), those within the highest GRS quintile had a nearly fourfold risk of CAD compared with those in the lowest GRS quintile, which also points toward the utility of the GRS in the early prediction of CAD.

Only a few studies have considered the association between GRSs and incidence of CAD in individuals with diabetes (33–35). Findings from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study in type 2 diabetes (35) showed that a GRS, derived from 204 variants identified in the general population, predicted CAD (area under receiver operating characteristic curve 0.567, HR per SD 1.27 [95% CI 1.18, 1.37]) comparable to our study; thus, providing further evidence for the known risk loci to impact individuals with type 1 diabetes equally. Moreover, addition of further genetic factors, such as the haptoglobin genotype (17) or diabetes-specific genetic findings (15,16), which are not included in our score, might further enhance the risk stratification of individuals with type 1 diabetes at increased risk of CAD. In line with the findings from the ACCORD study, the risk stratification improved modestly, but significantly, when an allelic GRS was added to the clinical model.

Over the past decade, research on the potential of genetic information to improve CAD risk prediction has expanded from a few candidate genes (14) to genome-wide studies with PRSs constructed with thousands or millions of genetic variants (19,20). In the current study, the allelic GRS with 156 established risk variants already provided significant improvement with respect to survival model performance. We also examined a general population PRS with 5 million variants, but found no significant improvement compared with the allelic GRS. The genetic background of CAD on a genome-wide level most likely differs for individuals with type 1 diabetes; therefore, using variant weights optimized in the general population, even at diabetes-specific genetic loci, might cause unnecessary noise and decrease PRS performance. We call for further research on diabetes-specific CAD genome-wide PRS.

In fact, in the general population, genome-wide PRSs of almost 500,000 adults (19) have shown great predictive ability of CAD events (C-index 0.623). Moreover, advances in microarray technologies may provide standardized genetic risk tools that can be applied to clinical use. Meanwhile, an allelic GRS may be helpful to identify individuals with type 1 diabetes with high genetic risk for CAD and to conduct randomized clinical trials to test whether these high-risk individuals are, similarly to the general population (21,22), more likely to benefit from early intervention.

Of note, we observed no difference in CAD risk between the top and the bottom quintile of the GRS among individuals with both antihypertensive and lipid-lowering drugs. Our results are consistent with previous post hoc analyses of clinical trial data, which have illustrated that high genetic risk of CAD may be mitigated by statin therapy (22,36). However, our findings may only partly be explained by the use of statins. Foremost, the number of individuals using statins without antihypertensive treatment was too low to be able to draw any firm conclusions from that group.
Additionally, our data show that individuals with antihypertensive and lipid-lowering treatment had already a worse clinical risk profile at baseline compared with those without pharmacological intervention throughout the follow-up. Following medical guidelines, antihypertensive and lipid-lowering drugs have been prescribed predominantly to those with the worst prognosis. Among these high-risk individuals with established clinical risk indications, the GRS no longer seems clinically useful.

Although our data on the GRS after manifestation of clinical symptoms and pharmacological interventions are inconclusive, the GRS is a life-long nonmodifiable risk factor for CAD, and therefore, high-risk individuals with respect to CAD could be identified prior to the manifestation of any clinical risk factor (37). Thus, a GRS may be a novel and independent biomarker for clinical use in CAD event prediction in the younger individuals with type 1 diabetes and allows preventative action and early intervention steps to be taken at an early stage among high-risk individuals (38).

The strengths of our study include its large representative cohort of individuals with type 1 diabetes. All participants were also carefully characterized and linked to the Finnish national administrative registers, covering all CAD events (39) and all outpatient prescriptions for antihypertensive and lipid-lowering drugs. Some limitations, however, need to be considered. Although we have one of the largest GWAS data sets for individuals with type 1 diabetes, this study might still suffer from limited power due to moderate GWAS size. Even though we used a validated clinical risk score developed for type 1 diabetes, the score was designed to predict CVD events, while we used MODAS as the primary outcome. Of note, this validated score does not include all verified clinical risk factors, such as LDL cholesterol (40). Owing to the observational design and limited power to match medicated and nonmedicated individuals with similar disease severity, we were not able to conclusively assess the effect of lipid-lowering medications.

In conclusion, our study showed that a general population GRS discriminates those individuals with type 1 diabetes who have high risk of CAD. Importantly, the GRS is an independent risk factor and comparable to the risk imposed by the traditional risk factors such as HbA1c and HDL and total cholesterol. Furthermore, the GRS modestly improved risk stratification when incorporated into the validated clinical risk model specific for individuals with type 1 diabetes. Notably, GRS is a particularly important risk factor among younger individuals, similarly to those with no medication, but seems to be no longer of clinical use in individuals with the worst clinical profile who are treated with both antihypertensive and lipid-lowering medications. As the GRS is a life-long risk factor and established well before the clinical risk manifests, we envision the main benefit in future clinical practice to be the early identification of younger individuals at a high risk for CAD.

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38. Lewis CM, Vassos E. Polygenic risk scores: from research tools to clinical instruments. Genome Med 2020;12:44