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# Predicting Subclinical Atherosclerosis in Adults with Type 1 Diabetes using Cardiovascular Risk Models: A Cross-Sectional Study from Italy

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**Research Insights**

**What is currently known about this topic?**

Patients with type 1 diabetes (T1D) are at increased risk for cardiovascular disease. Coronary computed tomography angiography (CCTA) and ultrasound measuring carotid intima-media thickness (cIMT) are non-invasive imaging tools for detecting subclinical atherosclerosis.

**What is the key research question?**

How effectively do current cardiovascular risk stratification models - specifically the 2019 Guidelines of the European Society of Cardiology (ESC), the Steno Type 1 Risk Engine (ST1RE), and the Scottish–Swedish risk prediction tool – discriminate the presence of subclinical coronary and carotid atherosclerotic disease in asymptomatic individuals with Type 1 Diabetes?

**What is new?**

Both ST1RE and the Scottish–Swedish risk tools showed good discrimination for imaging-defined subclinical atherosclerosis, including CCTA.

**How might this study influence clinical practice?**

The findings could help triage asymptomatic adults with T1D for cardiovascular imaging; prospective validation against imaging endpoints is warranted.



**Abstract**

**Background**

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among individuals with type 1 diabetes (T1D); nevertheless, cardiovascular risk stratification remains an unmet need in T1D. Cardiovascular risk tools

were developed to predict 10-year clinical events. Whether they identify subclinical atherosclerosis - a potential gatekeeper for intensified prevention - remains uncertain.

**Methods**

We conducted a cross-sectional analysis of consecutive T1D adults without a history of CVD enrolled at a secondary centre in Italy. All participants underwent coronary computed tomography angiography (CCTA) and carotid ultrasound. The primary outcome was a composite imaging endpoint, defined as any coronary plaque on CCTA and/or maximum carotid intima-media thickness ($cIMT_{max}$) ≥1.5 mm. We compared the performance of T1D-specific CV risk models (2019 European Society of Cardiology [ESC] Guidelines, Steno Type 1 Risk Engine [ST1RE], and Scottish-Swedish CVD risk prediction tool) in predicting the presence of subclinical atherosclerosis. Discrimination was assessed using the Area Under the receiver operating characteristic Curve (AUC), and differences between AUCs were evaluated using the DeLong test; calibration was visualised with calibration plots and summarised by Brier score. Sensitivity analyses evaluated CCTA-only and carotid-only endpoints.

**Results**

One hundred and one patients (52.5% males) were included in the study, with a mean age of 45±13 years and a median diabetes duration of 21 years (Q1–Q3 13; 32). The composite imaging endpoint occurred in 66/101 (65.4%); 55 patients (54.5%) had coronary plaques, and 41 patients (40.6%) presented

$cIMT_{max}$ above threshold. Both ST1RE and the Scottish-Swedish risk scores showed strong discrimination for the combined imaging endpoint (AUC 0.899 and 0.907, respectively). Apparent calibration to the imaging endpoint was acceptable, with Brier scores of 0.126 for ST1RE and 0.128 for the Scottish-Swedish model.

**Conclusions**

In an Italian cohort of asymptomatic T1D adults, T1D-specific risk scores demonstrated a strong discrimination ability for imaging-defined subclinical atherosclerosis. Theymight help triage asymptomatic individuals who could benefit from targeted cardiovascular imaging in specific settings. Since these tools predict events rather than imaging findings, recalibration and prospective validation against imaging endpoints are needed before using predicted probabilities as absolute risks informing clinical decision-making.

**Trial registration**

ClinicalTrials.gov Identifier: NCT06290544. Registered on 29 February 2024.



## Introduction

Individuals with type 1 diabetes mellitus (T1D) face a heightened risk of cardiovascular disease (CVD) compared to the general population, resulting in higher morbidity and premature mortality [1]. Large epidemiological studies have shown that people with T1D experience a markedly reduced life expectancy and a significantly increased risk of coronary artery disease (CAD), myocardial infarction, stroke, and heart failure, particularly when

diabetes onset occurs early in life [2]. All-cause mortality shows a similar trend [2].

The excess cardiovascular risk in T1D is likely driven by a complex interplay between conventional risk factors and diabetes-specific features, including chronic hyperglycaemia, inflammation, dyslipidaemia, and hypertension. However, the relative contribution of these factors and the heterogeneity of cumulative glycaemic exposure make individual cardiovascular risk estimation particularly challenging in this population.

European Society of Cardiology (ESC) guidelines [3-6] primarily stratify cardiovascular risk in diabetes using categorical approaches based on disease duration, target organ damage and the presence of additional risk factors, offering only limited differentiation between type 1 and type 2 diabetes. In contrast, several cardiovascular risk prediction tools have been specifically developed to improve risk stratification in individuals with T1D. The Steno Type 1 Risk Engine (ST1RE) [7] was designed to estimate the risk of first cardiovascular event in adults with T1D. More recently, the Scottish–Swedish cardiovascular risk model [8] was developed and incorporated into the 2023 ESC guidelines, receiving a class IIb recommendation (level of evidence B) for cardiovascular risk estimation in individuals with T1D [9]. Both these risk engines were primarily derived and validated only in Northern European cohorts; their applicability in Mediterranean populations remains uncertain. Preliminary studies on smaller cohorts have suggested a potential association between individual risk estimates and the presence of subclinical

atherosclerosis [10-13]. In this context, imaging techniques such as coronary computed tomography angiography (CCTA) and carotid ultrasound provide a robust clinical benchmark by allowing direct detection of early vascular disease and may help refine cardiovascular risk stratification in asymptomatic individuals [14-15].

The aim of the present study was therefore to evaluate the performance of three cardiovascular risk stratification models - the 2019 ESC risk classification, the ST1RE, and the Scottish–Swedish risk prediction model - in discriminating the presence of subclinical coronary and/or carotid atherosclerosis in an Italian cohort of asymptomatic individuals with T1D. To this end, consecutively enrolled T1D patients underwent coronary computed tomography angiography (CCTA) and B-mode carotid ultrasound.

## Methods

### *Study design and population*

"Cardiovascular risk assessment in patients with T1D" (CARDT1) is a prospective, multi-centre study designed to assess the prevalence of CVD and to evaluate vascular damage in T1D patients (https://clinicaltrials.gov/study/NCT06290544). The study was approved by the local Ethics Committee (Comitato Etico degli IRCCS Istituto Europeo di Oncologia e Centro Cardiologico Monzino – ID R1478/21-CCM 1552, approved on 21st June 2021) and performed according to the principles established by the 1975 Declaration of Helsinki. All participants gave written informed consent. In this pilot work, we performed a single-centre, cross-

sectional analysis of consecutive adults (≥18 years) with T1D attending the Centro Cardiologico Monzino IRCCS (Milan, Italy), enrolled between November 2021 and May 2025. Exclusion criteria were prior clinical CVD (history of CAD, including myocardial infarction, symptomatic angina, or coronary revascularisation; cerebrovascular disease, including stroke or transient ischemic attack or carotid revascularisation; peripheral arterial disease), contraindications to CCTA, non-autoimmune diabetes, and pregnancy.

*Anthropometric, clinical, and metabolic variables*

At enrolment, participants underwent a comprehensive outpatient clinical evaluation and data on demographic and anthropometric variables, medical history, lifestyle habits, diabetes management, and medications were collected. Laboratory measurements included glycated haemoglobin (HbA1c), creatinine, and urinary albumin-to-creatinine ratio (UACR), total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), triglycerides, lipoprotein(a) [Lp(a)], and apolipoprotein B (ApoB). These data were collected at the time of the first visit or retrieved from medical charts (no more than 3 months from enrolment). The estimated Glomerular Filtration Rate (eGFR) was derived using the Chronic Kidney Disease Epidemiology Collaboration standard equation [16]; LDL-cholesterol was derived using the Friedewald equation [17].

Average HbA1c over the previous 5 years and occurrence of microvascular complications were retrieved from electronic medical charts or medical reports. Diabetic nephropathy was diagnosed if the spot UACR was >30 mg/g and/or eGFR was <60 mL/min/1.73 $m^2$. Neuropathy was noted if patients reported symptoms, diagnostic tests, when available, or specific treatments. In addition, intermittent or continuous glucose monitoring data were collected for each patient.

*Cardiovascular risk scores*

We assessed each participant's cardiovascular risk using (i) the 2019 ESC risk stratification for T1D, (ii) ST1RE (https://steno.shinyapps.io/T1RiskEngine), and (iii) the Scottish–Swedish risk score (https://diabepi.shinyapps.io/cvdrisk/), following published algorithms [3,7,8]. As deprivation index data are fragmented and lack timely updates across the Italian territory, the Scottish-Swedish Risk score was also calculated using the formula without its inclusion, as specifically provided by the original Authors [8]. This adaptation ensures the model's applicability even in regions where granular socioeconomic data are unavailable, maintaining the score's predictive reliability.

The 2019 ESC risk classification was included as a term of comparison as it was the most commonly applied framework during the study period and remains the reference used in the existing literature on the topic [10-13]. The 2019 ESC risk stratification system classifies individuals with diabetes (either type 1 or type 2) as at moderate, high, and very high risk, according to age,

diabetes duration, presence of target organ damage and additional cardiovascular risk factors. When a participant could reasonably fit two adjacent ESC categories for borderline clinical features, the lower category was consistently assigned.

When incorporating the ST1RE and Scottish-Swedish risk prediction scores as categorical variables, we used the 2023 ESC guidelines as a reference [9]. Patients were therefore categorised in four groups: low risk, when the probability of an event occurring within 10 years was less than 5%; moderate risk, with a probability between 5% and 10%; high risk, with a probability between 10% and 20%; and very high risk, with a probability of 20% or higher. Patients with severe target organ damage, as defined in 2023 ESC guidelines, were included in the very high-risk category. These thresholds were used only to provide a clinically interpretable framework aligned with guideline-based risk stratification and to allow comparison with ESC risk categories.



In addition to this, we have included the SCORE2-Diabetes risk assessment tool [18] as a further point of comparison, given its relevance within the current ESC guidelines on cardiovascular prevention, albeit on an exploratory basis only. SCORE2-Diabetes, in fact, was developed specifically for individuals with type 2 diabetes and its applicability is limited to the 40–69 age group.

*Coronary and carotid atherosclerosis assessment*

All CCTAs were performed using a 256-detector row scanner capable of whole-heart coverage in one beat (Revolution CT, GE Healthcare, Milwaukee, WI), with 0.23 mm spatial resolution, 0.28 s gantry rotation time, and an intracycle motion-correction algorithm for addressing motion artefacts. A Z-axis coverage of 16 cm was used for all patients. An ECG-synchronised rest CCTA scan was conducted according to the recommendations of the Society of Cardiovascular Computed Tomography [19]. All patients received a 50 ml bolus of Iodixanol 320 (Visipaque 320 mg/ml, GE Healthcare) at an infusion rate of 5 ml/s, followed by 50 ml of saline solution. All patients received sublingual nitrates to ensure coronary vasodilation and β-blockers, when necessary, to limit the heart rhythm to approximately 65 bpm. The dataset from each CCTA examination was transferred to an image-processing workstation (Advantage Workstation Version 4.7, GE Healthcare) and analysed by two readers who were blinded to the patients' clinical data and who had more than 10 years' experience in CCTA analysis. For any disagreement, a joint reading was performed, and a consensus decision was reached. Each coronary segment was evaluated for the presence of atherosclerotic plaques. Segments with severe motion artefacts, blooming artefacts, or insufficient image quality preventing reliable evaluation were considered non-diagnostic and excluded from analysis (<1% of all segments). A coronary plaque was defined as any structure clearly assignable to the coronary artery wall that could be distinguished from the lumen and

surrounding pericardial tissue, and that had a cross-sectional area ≥1 $mm^2$. Calcified, non-calcified and mixed plaques were all considered.

Subclinical coronary atherosclerosis was defined as the presence of any detectable plaque in any coronary segment. Patients were also stratified according to coronary obstruction severity (i.e., no coronary plaques, non-obstructive coronary disease when the maximum stenosis was <50%, and obstructive coronary disease when at least one stenosis was ≥50%). The Coronary Artery Calcium (CAC) score was quantified using the Agatston method, expressed in Hounsfield Units (HU) [20].

B-mode ultrasound of carotid arteries was performed with a specific protocol, extensively reported elsewhere [21], by a team of experts. Briefly, the same machine (Esaote MyLabTwice) was used for all patients equipped with a 5 to 10-MHz linear array probe. The far walls of the left and right common carotids, bifurcations, and internal carotid arteries were visualised at 3 scan angles (lateral, anterior, and posterior). Each segment was measured in at least 2 different frames. Subclinical carotid artery disease was defined according to the Mannheim consensus plaque criterion as $cIMT_{max}$ ≥1.5 mm, measured from the media–adventitia interface to the intima–lumen interface [22].



*Outcomes*

All outcomes evaluated in this study refer to imaging-defined subclinical atherosclerosis. The primary endpoint was a composite imaging endpoint defined as the presence of subclinical atherosclerosis in at least one vascular

territory: coronary plaque detected by CCTA and/or carotid plaque defined as $cIMT_{max}$ ≥1.5 mm on carotid ultrasound.

*Statistical Analysis*

Continuous variables were expressed as mean ± standard deviation (SD) if normally distributed, otherwise as median and first and third quartiles (Q1–Q3). Categorical variables were presented as counts and percentages. Comparisons between two groups were performed using Student's t-test or Wilcoxon-Mann-Whitney test for continuous variables, and Chi-square test or Fisher’s exact test for categorical variables. The agreement among the different risk equations was evaluated using Cohen’s weighted kappa coefficient. The association between risk estimates and the observed subclinical coronary and/or carotid atherosclerosis was assessed using a logistic regression model. Predictive performance of the different risk estimation scores was assessed using Receiver Operating Characteristic (ROC) curve analysis, discrimination was quantified by the Area Under the ROC Curve (AUC), reported as point estimates with 95% confidence intervals obtained using percentile bootstrap resampling (500 iterations). Differences between AUCs were tested using the DeLong test. Calibration was assessed using the Brier score and visualised with calibration plots comparing predicted and observed outcome probabilities for the imaging-defined outcome for the ST1RE and Scottish-Swedish risk prediction tools. Additionally, the Hosmer-Lemeshow Goodness-of-Fit test was used to assess model calibration. The interobserver agreement for the detection of

significant CAD was tested with Cohen's kappa. Additional analyses were performed considering CAC score > 0 as an outcome. All tests were two-sided, and a p-value of <0.05 was considered statistically significant. Statistical analysis was performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

Assuming an outcome prevalence of 60%, a sample of 100 subjects provided 80% statistical power to detect an AUC of at least 0.75, with a 95% confidence interval between 0.66 and 0.84.

**Results**

Of the 128 patients enrolled in the CARDT1 study so far, eight patients were excluded for a previous cardiovascular event. Only asymptomatic patients who underwent both CCTA and carotid ultrasound (N = 101, 52.5% males) were included in this study, as shown in Figure 1. Complete clinical characteristics are reported in Table 1. Median diabetes duration was 21 years (Q1–Q3 13, 32 years), and 37% of patients were on continuous subcutaneous insulin infusion (CSII) treatment.

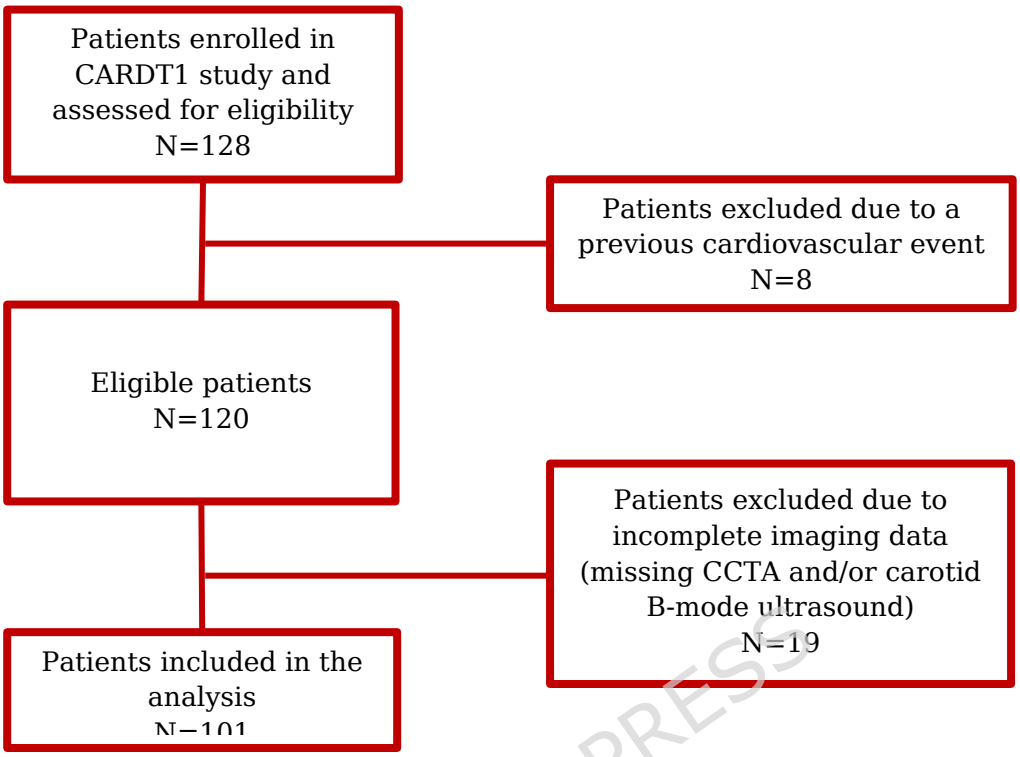


**Figure 1.** Flowchart of patient enrolment in the CARDT1 study

**Table 1.** Clinical features of the study population, stratified into two groups based on the presence of subclinical coronary or carotid atherosclerosis

| Characteristic | Overall Cohort | Patients without the composite imaging endpoint | Patients with the composite imaging endpoint | p |
|---|---|---|---|---|
| | (N = 101) | (N = 35) | (N = 66) | |
| **Sex** (Male), n (%) | 53 (52.5%) | 14 (40%) | 39 (59.1%) | 0.07 |
| **Age** (years) | 45.3±12.8 | 34.1±8.5 | 51.2±10.5 | <0.001 |
| **BMI** (kg/m$^2$) | 24.5±3.6 | 23.5±3.7 | 25.04±3.4 | 0.039 |
| **Diabetes duration** (years) | 21 (13–32) | 18 (12–30) | 22 (14–36) | 0.13 |
| **HbA1c** (%) | 7.02±0.96 | 6.81±0.83 | 7.14±1.02 | 0.13 |
| **eGFR** (mL/min/1.73m$^2$) | 99.5±13.4 | 104.7±13.7 | 96.7±12.4 | 0.004 |
| **Total cholesterol** (mg/dL) | 176.4±31.5 | 179.0±31.8 | 175.0±31.5 | 0.55 |

| | | | | |
|---|---|---|---|---|
| **HDL** (mg/dL) | 62.8±18.7 | 63.3±13.6 | 62.6±20.9 | 0.86 |
| **Triglycerides** (mg/dL) | 73 (56–96) | 71 (54–92) | 74 (57–96) | 0.49 |
| **LDL** (mg/dL) | 97.2±26.3 | 99.9±28.5 | 95.8±25.2 | 0.47 |
| **SBP** (mmHg) | 121±14 | 113±11 | 125±13 | <0.001 |
| **Smoke**, n (%) | 24 (23.8%) | 7 (20%) | 17 (25.8%) | 0.52 |
| **Regular physical exercise,** n (%) | 32 (31.7%) | 13 (37.1%) | 19 (28.8%) | 0.39 |
| **Normal ACR,** n (%) | 95 (95%) | 35 (100%) | 60 (92.3%) | 0.16 |
| **Macroalbuminuria**, n (%) | 0 (0%) | 0 (0%) | 0 (0%) | 1.00 |
| **Microalbuminuria**, n (%) | 6 (5.9%) | 0 (0%) | 6 (9.1%) | 0.09 |
| **Mild/moderate retinopathy**, n (%) | 17 (16.8%) | 6 (17.1%) | 11 (16.7%) | 0.95 |
| **Neuropathy**, n (%) | 7 (6.9%) | 1 (2.9%) | 6 (9.1%) | 0.42 |
| **Autonomic neuropathy**, n (%) | 3 (3.0%) | 0 (0%) | 3 (4.5%) | 0.55 |
| **Any microvascular complication**, n (%) | 34 (33.7%) | 8 (22.9%) | 26 (39.4%) | 0.09 |
| **Treated for dyslipidaemia**, n (%) | 40 (39.6%) | 3 (8.6%) | 37 (56.1%) | <0.001 |
| **Treated for hypertension**, n (%) | 19 (18.8%) | 0 (0%) | 19 (28.8%) | <0.001 |
| **Total insulin daily dose** (unit/kg/day) | 0.54±0.20 | 0.50±0.19 | 0.56±0.20 | 0.21 |
| **Insulin pump use**, n (%) | 37 (37.0) | 18 (51.4%) | 19 (29.2%) | 0.028 |
| **LADA**, n (%) | 11 (11.3) | 2 (5.9%) | 9 (14.3%) | 0.32 |
| **Apo B** (mg/dL) | 67 (60–75) | 72 (61–81) | 64 (58–72) | 0.09 |
| **Lp(a)** (mg/dL) | 11.2 (5.0–21.6) | 9.9 (5.0–20.1) | 11.5 (5.0–24.0) | 0.58 |
| **ST1RE** (%) | 9.8 (4.2–17.8) | 3.6 (2.5–6.1) | 13.3 (8.7–21.1) | <0.001 |
| **Scottish-Swedish** (%) | 7.0 (3.0–14.4) | 2.5 (1.8–4.8) | 10.4 (6.6–19.0) | <0.001 |
| **Scottish-Swedish no DI** (%) | 7.1 (3.3–15.2) | 2.9 (2.0–5.0) | 12.1 (6.4–21.8) | <0.001 |
| **Calcium score** (Agatston Unit) | 0 (0–16) | 0 (0–0) | 4 (0–42) | <0.001 |
| **Calcium score > 0 AU**, n (%) | 30 (33.0%) | 0 (0%) | 30 (53.6%) | <0.001 |

Values are presented as mean ± standard deviation (SD), median and interquartile range (Q1–Q3), or counts and proportions, as appropriate. Composite imaging endpoint: subclinical coronary or carotid atherosclerosis. Any microvascular complication is defined as the presence of at least one of the following: microalbuminuria, any grade of retinopathy, or autonomic/peripheral neuropathy. No patients showed eGFR<60 ml/min/$m^2$.

Abbreviations: BMI, body mass index; HbA1c, glycated haemoglobin; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; SBP, systolic blood pressure; LADA, Latent Autoimmune Diabetes in Adults; Apo B, apolipoprotein B; Lp(a), lipoprotein (a); ST1RE, Steno Type 1 Risk Engine; Scottish-Swedish, Scottish-Swedish cardiovascular disease (CVD) risk prediction tool; Scottish-Swedish no DI, Scottish-Swedish CVD risk prediction tool without Deprivation Index; AU, Agatston Unit.

Imaging-defined subclinical atherosclerosis (composite endpoint) was present in 66/101 participants (65.4%). It is noteworthy that the present cohort comprised 38 diabetic patients aged under 40, of whom 11 (29%) exhibited signs of atherosclerosis. Coronary plaques were detected in 55 patients (54.5%), whereas carotid disease defined as $cIMT_{max} \geq 1.5$ mm was observed in 41 patients (40.6%). Patients diagnosed with subclinical coronary and/or carotid atherosclerosis were significantly older ($p < 0.001$), had a higher Body Mass Index (BMI) ($p = 0.039$), and exhibited higher systolic blood pressure ($p < 0.001$) and lower eGFR ($p = 0.004$). Additionally, a higher proportion of these patients had been treated for hypertension and dyslipidaemia ($p < 0.001$), and a lower proportion had been treated with CSII therapy ($p = 0.028$) (Table 1). No significant differences were observed between T1D patients with or those without subclinical atherosclerosis with respect to sex, smoking habits, the presence of nephropathy, retinopathy and

neuropathy, lipid profile (total cholesterol, LDL-cholesterol, HDL-cholesterol, lipoprotein(a), apolipoprotein B) and total daily insulin dose. None of the 2-week ambulatory glucose profiles (AGPs) parameters obtained by continuous glucose monitoring (CGM) showed a correlation with atherosclerosis (Supplementary Table 1).

According to the 2019 ESC categories, 28 (27.7%) patients were at moderate risk, 8 (7.9%) at high risk, and 65 (64.4%) at very high risk of cardiovascular events. Figure 2 shows the distributions of patients based on risk stratification using the ST1RE and Scottish-Swedish risk prediction tool. The median risk of 10-year cardiovascular events estimated with ST1RE was 9.8% (Q1–Q3: 4.2-17.8), with a range of 1.5% to 41.6%; the median 10-year cardiovascular risk estimated with the Scottish-Swedish prediction tool was 7.0% (Q1–Q3: 3.0-14.4), with a range of 0.7% to 65.4%. The agreement between ST1RE and the Scottish–Swedish risk score was substantial (weighted κ = 0.690; 95% CI: 0.599–0.780), indicating good concordance in patient classification across risk categories. In contrast, the agreement between the 2019 ESC risk stratification and ST1RE and Scottish-Swedish score was low (weighted κ = 0.204; 95% CI: 0.098–0.309 and weighted κ = 0.164; 95% CI: 0.069–0.258, respectively) (Supplementary Table 2).

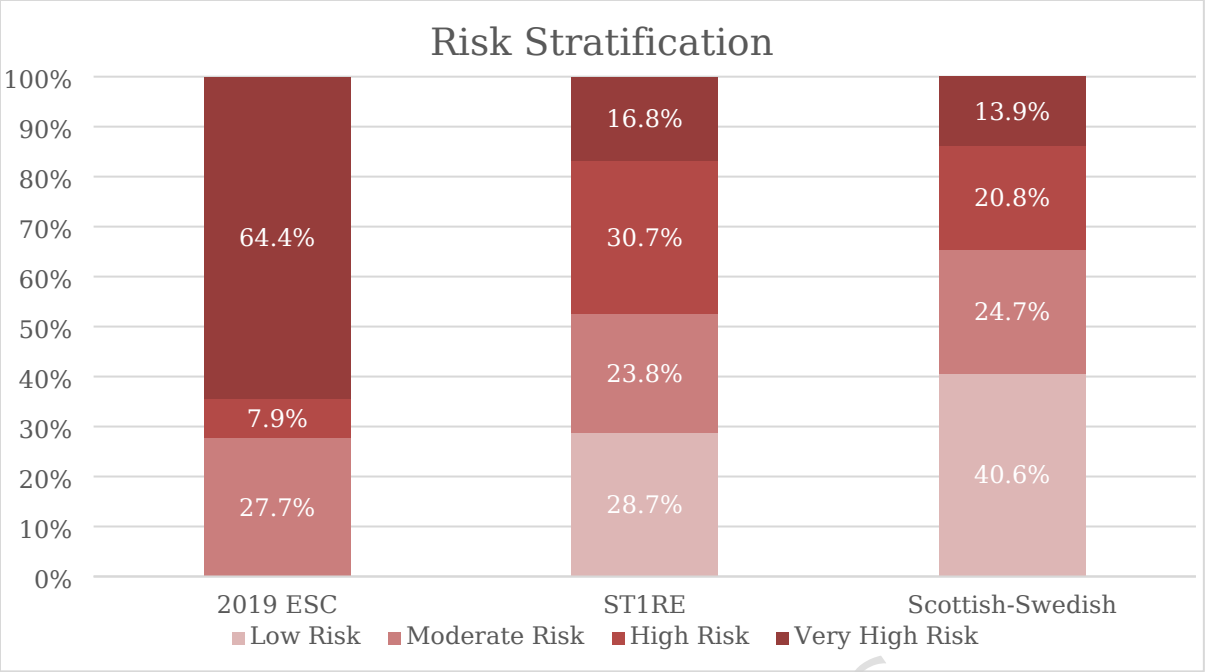


**Figure 2.** Proportions of patients stratified by estimated cardiovascular risk based on risk scoring models. Abbreviations: 2019 ESC, 2019 European Society of Cardiology risk stratification guidelines; ST1RE, Steno Type 1 Risk Engine; Scottish-Swedish, Scottish-Swedish CVD risk prediction tool.

At CCTA, 46 patients (45.5%) had no CAD, 45 (44.6%) showed non-obstructive disease, and 10 (9.9%) had obstructive disease. The κ value for detection of significant CAD was 0.95 for interobserver agreement. The 2019 ESC risk stratification did not correlate with the presence of subclinical coronary atherosclerosis; conversely, ST1RE and Scottish-Swedish prediction tools showed a significant association between risk stratification categories and the presence of CAD (Table 2).

**Table 2.** Comparison of risk assessment models between groups stratified according to CCTA results

| | **No CAD** (N=46) | **Non-ob-CAD** (N=45) | **Ob-CAD** (N=10) | **p** |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| **2019 ESC,** n (%) | | | | |
| MEDIUM Risk | 18 (39.1%) | 9 (20%) | 1 (10%) | 0.13 |
| HIGH Risk | 4 (8.7%) | 4 (8.9%) | 0 (0%) | |
| VERY HIGH Risk | 24 (52.2%) | 32 (71.1%) | 9 (90%) | |
| **ST1RE,** n (%) | | | | |
| LOW risk | 23 (50%) | 6 (13.3%) | 0 (0%) | <.001 |
| MEDIUM risk | 14 (30.5%) | 10 (22.2%) | 0 (0%) | |
| HIGH risk | 6 (13%) | 20 (44.5%) | 5 (50%) | |
| VERY HIGH risk | 3 (6.5%) | 9 (20%) | 5 (50%) | |
| **Scottish-Swedish,** n (%) | | | | |
| LOW risk | 33 (71.7%) | 8 (17.8%) | 0 (0%) | <.001 |
| MEDIUM risk | 9 (19.6%) | 14 (31.1%) | 2 (20%) | |
| HIGH risk | 3 (6.5%) | 13 (28.9%) | 5 (50%) | |
| VERY HIGH risk | 1 (2.2%) | 10 (22.2%) | 3 (30%) | |

P-value represents the result of Fisher's exact test. Abbreviations: CCTA, coronary computed tomography angiography; no CAD, no coronary plaques; non-ob-CAD, non-obstructive coronary artery disease; ob-CAD, obstructive coronary artery disease; 2019 ESC, 2019 European Society of Cardiology risk stratification guidelines; ST1RE, Steno Type 1 Risk Engine; Scottish-Swedish, Scottish-Swedish cardiovascular disease risk prediction tool.



Of note, the 2019 ESC stratification classified one patient with obstructive disease below the high-risk threshold, whereas all patients with obstructive disease were classified as at least high risk by ST1RE. Moreover, the ST1RE score, and to a greater extent the Scottish-Swedish score, classified a smaller proportion of patients with a negative CCTA as being at high or very high risk than the 2019 ESC stratification did.

Both T1D-specific risk scores were significantly associated with subclinical coronary and carotid atherosclerosis, as well as with the combined imaging endpoint (Table 3). On the contrary, the 2019 ESC risk stratification showed

no significant association with the presence of subclinical coronary or carotid atherosclerosis, nor with the combined imaging endpoint (Table 3).

The 2019 ESC risk stratification, ST1RE, and Scottish-Swedish risk scores were tested using ROC curve analysis to assess their accuracy in predicting the presence of subclinical carotid and/or coronary atherosclerosis. The ST1RE and Scottish-Swedish tools demonstrated the best discriminative performance across all outcomes (Table 3). For subclinical coronary atherosclerosis, the AUC of ST1RE and the Scottish-Swedish tool was 0.831 and 0.862, respectively; similarly, for subclinical carotid atherosclerosis, the AUC values were 0.816 and 0.798, respectively. The best performance was observed when coronary and carotid diseases were considered combined, with an AUC of 0.899 for ST1RE and 0.907 for the Scottish-Swedish score. These tools showed superior discriminative performance compared to cardiovascular risk stratification based on the 2019 ESC guidelines ($p < 0.001$ for all AUC comparisons - Figure 3), while no significant differences were found between ST1RE and the Scottish-Swedish score in discriminating subclinical coronary atherosclerosis ($p = 0.104$), carotid atherosclerosis ($p = 0.357$) or the combined endpoint ($p = 0.652$).

Given that the T1D-specific scores are continuous risk estimates and may therefore inherently contain more information than the categorical classification used in the 2019 ESC guidelines, we stratified the ST1RE and Scottish–Swedish scores into four classes using thresholds based on the 2023 ESC guidelines, to make a fairer comparison. Their association with imaging

endpoints remained significant (Supplementary Table 3 and Supplementary Figure 1), suggesting that their performance is not explained solely by scale granularity, but, more importantly, by their disease-specific design.

In addition, we conducted an exploratory analysis using a state-of-the-art diabetes risk score such as SCORE2-Diabetes, although this is specific to type 2 diabetes and limited to the 40–69 age group. By excluding the 38 patients under the age of 40 and the 2 over the age of 69, and then comparing the 4 models across the 61 subjects in the relevant age group, SCORE2-Diabetes showed discriminatory ability comparable to that of T1D-specific risk models for all imaging endpoints (Supplementary Figure 2). However, the reduction in sample size and clinical variability led to a downward levelling of the models' predictive performance.

Finally, both ST1RE and Scottish–Swedish scores, but not the 2019 ESC stratification, were significantly associated with the presence of coronary artery calcium (CAC score > 0; Supplementary Table 4), which was observed in 33% of the study population as assessed by CCTA. Results were confirmed even when excluding the deprivation index from the Scottish–Swedish model, and when both T1D-specific risk engines were stratified as categorical variables (Supplementary Table 4).



**Table 3.** Association and predictive performance of the 2019 ESC stratification, ST1RE and Scottish-Swedish risk models in relation to subclinical coronary and carotid atherosclerosis and the imaging-based composite endpoint

| Outcome | Effect | OR | 95% CI (Lower, Upper) | p (OR) | AUC | 95% CI Bootstrap | p (Hosmer- | Brier |
|---|---|---|---|---|---|---|---|---|

| | | | | | | (Lower, Upper) | Lemeshow) | Score |
|---|---|---|---|---|---|---|---|---|
| **Subclinical coronary atherosclerosis** | 2019 ESC | 1.75 | (1.11, 2.77) | 0.016 | 0.618 | (0.519, 0.720) | 0.97 | 0.233 |
| | ST1RE | 1.16 | (1.08, 1.25) | <0.001 | 0.831 | (0.744, 0.907) | 0.002 | 0.176 |
| | Scottish-Swedish | 1.23 | (1.11, 1.36) | <0.001 | 0.862 | (0.782, 0.927) | <0.001 | 0.160 |
| **Subclinical carotid atherosclerosis** | 2019 ESC | 1.24 | (0.78, 1.95) | 0.360 | 0.549 | (0.500, 0.656) | 0.40 | 0.239 |
| | ST1RE | 1.14 | (1.07, 1.21) | <0.001 | 0.816 | (0.729, 0.890) | 0.56 | 0.179 |
| | Scottish-Swedish | 1.10 | (1.04, 1.15) | <0.001 | 0.798 | (0.708, 0.877) | 0.004 | 0.200 |
| **Composite imaging endpoint** | 2019 ESC | 1.37 | (0.87, 2.16) | 0.17 | 0.566 | (0.504, 0.669) | 0.46 | 0.222 |
| | ST1RE | 1.43 | (1.22, 1.66) | <0.001 | 0.899 | (0.830, 0.953) | 0.10 | 0.126 |
| | Scottish-Swedish | 1.60 | (1.30, 1.98) | <0.001 | 0.907 | (0.852, 0.959) | 0.049 | 0.128 |

The table reports: odds ratios (OR) with corresponding 95% confidence intervals (CI) and p-values; discrimination performance (Area Under the ROC Curve, AUC) with corresponding 95% bootstrap CI; calibration (Hosmer–Lemeshow test), and Brier scores. Composite imaging endpoint: subclinical coronary or carotid atherosclerosis. Abbreviations: 2019 ESC, 2019 European Society of Cardiology risk stratification guidelines; ST1RE, Steno Type 1 Risk Engine; Scottish-Swedish, Scottish-Swedish cardiovascular disease (CVD) risk prediction tool; Scottish-Swedish no DI, Scottish-Swedish CVD risk prediction tool without Deprivation Index.

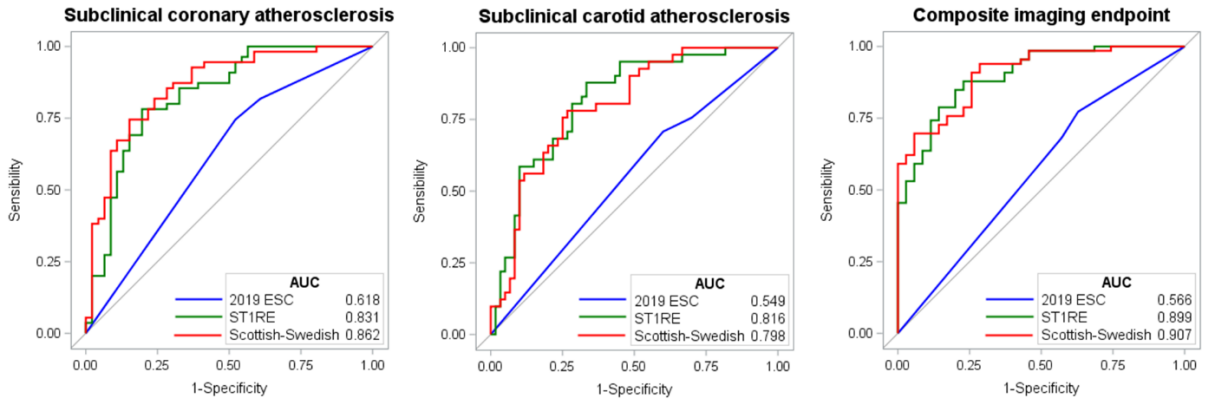


**Figure 3.** Assessment of the accuracy of the risk models in predicting the presence of subclinical coronary and/or carotid atherosclerosis. The accuracy of the 2019 ESC stratification model (blue line), ST1RE (green line) and the Scottish-Swedish risk prediction tool (red line) in discriminating the presence of subclinical coronary atherosclerosis (panel A), subclinical carotid atherosclerosis (panel B), and the composite imaging endpoint (panel C) was assessed using the ROC curve analysis. Composite imaging endpoint: subclinical coronary and/or carotid atherosclerosis. Abbreviations: AUC, Area Under ROC Curve; 2019 ESC, 2019 European Society of Cardiology risk stratification guidelines; ST1RE, Steno Type 1 Risk Engine; Scottish-Swedish, Scottish-Swedish cardiovascular disease risk prediction tool.

When evaluating calibration (Supplementary Figure 3), not all models demonstrated adequate fit. For subclinical coronary atherosclerosis, the ST1RE and Scottish-Swedish scores showed relatively low Brier scores (0.176 and 0.160, respectively) but significant p-values for Hosmer–Lemeshow test ($p = 0.002$ and $p < 0.001$), indicating suboptimal calibration despite acceptable overall accuracy. A similar pattern was observed for subclinical carotid atherosclerosis, with Brier scores of 0.179 (ST1RE) and 0.200 (Scottish-Swedish), while Hosmer–Lemeshow p-values were 0.56 and 0.004, respectively. In contrast, both models showed their best calibration for the combined imaging endpoint, where lower Brier scores (0.126 for ST1RE and

0.128 for the Scottish-Swedish model); Hosmer–Lemeshow test was non-significant for ST1RE (p = 0.10), whereas it reached statistical significance for the Scottish-Swedish model (p = 0.049) (Table 3).

**Discussion**

To our knowledge, this is the first study to apply cardiovascular risk models for T1D to assess the occurrence of subclinical coronary atherosclerosis detected by CCTA, and the first to apply the Scottish-Swedish risk model in an Italian cohort of asymptomatic patients with T1D. Importantly, our analysis did not aim to validate ST1RE and the Scottish-Swedish risk model for predicting cardiovascular events, but rather to explore their ability to identify individuals with imaging evidence of subclinical atherosclerosis. The assessment was conducted using both CCTA and carotid B-mode ultrasound in two of the most relevant vascular sites. Our findings confirm that atherosclerosis is highly prevalent in T1D patients, as 65.4% of our cohort showed either carotid or coronary artery disease, and this prevalence correlates with age.

This study shows that both ST1RE and the Scottish–Swedish models exhibit high and comparable discriminatory ability in detecting imaging-defined subclinical atherosclerosis in this cohort, whereas the risk stratification proposed in the 2019 ESC guidelines does not. These findings support the potential utility of T1D-specific tools for identifying patients at higher risk for coronary and/or carotid atherosclerotic involvement, who may therefore benefit most from tailored cardiovascular diagnostic/therapeutic

management. Our findings are consistent with the previously observed correlation between the presence of carotid plaque and the risk category assigned by ST1RE in Italian cohorts [10,11] and other Mediterranean populations [12,13]; likewise, our results confirm previous findings of poor concordance between 2019 ESC risk classification and ST1RE prediction [23].

As expected, in our cohort, older patients have a higher likelihood of atherosclerotic disease. Since age is a major determinant of atherosclerosis and cardiovascular disease, the superior performance of ST1RE and the Scottish-Swedish score is likely due to their ability to attribute greater weight to age and its correlates, thereby correctly identifying younger patients with a lower probability of imaging-defined disease, beyond diabetes duration alone. However, it is plausible that these same patients may develop detectable atherosclerosis over time. Indeed, patients with subclinical atherosclerosis, being on average older, had higher blood pressure values, a higher BMI, and a reduced eGFR, and were more likely to be prescribed antihypertensive and lipid-lowering medications. Those observations suggest that their increased risk had been recognised on a clinical basis, given that the imaging investigations the patients underwent at study enrolment were the first for all of them. This may provide a rationale for the absence of an association between LDL-cholesterol and atherosclerotic burden in this study. Consistently, smoking habits and lipid profile were not linked to the presence of atherosclerosis, underscoring the complexity of cardiovascular

risk management in T1D patients and highlighting the importance of careful, personalised screening.

Furthermore, good glycaemic control, demonstrated in both study groups, suggests that a significant proportion of subclinical atherosclerosis is attributable to diabetes- or non-diabetes-related parameters that have not yet been clarified. On the other hand, continuous glucose monitoring metrics were derived from a short observational window preceding enrolment and therefore may not fully reflect long-term glycaemic exposure, which is more relevant for the development of atherosclerosis over decades. We cannot rule out that the assessment of CGM metrics over longer periods may be informative for possible associations with subclinical atherosclerosis.

It is noteworthy that an exploratory analysis employing SCORE2-Diabetes as a comparator (and therefore restricted to a subgroup of patients aged 40-69) showed similar predictive performance between this model, developed for type 2 diabetes, and the two models specific to T1D. This outcome was anticipated, given the three models share pertinent variables such as diabetes duration, HbA1c, and eGFR, along with traditional cardiovascular risk factors. Although at the expense of power and discriminatory ability, this finding reinforces the notion that the incorporation and appropriate weighting of diabetes-related variables enhance the identification of subclinical atherosclerosis. It is evident that SCORE2-Diabetes is not clinically applicable to patients with T1D, as it has been specifically calibrated

and validated for type 2 diabetes. Moreover, this score is not applicable to younger age groups, in which T1D is ordinarily diagnosed.

This study has several limitations. First, the relatively small sample size may limit the statistical precision of the estimates and the generalizability of the findings; in addition, the calibration analysis, relying on this limited sample, should be interpreted with caution.

Regarding the imaging assessment, our definition of coronary atherosclerosis included minimal lesions. While these provide a comprehensive view of early vascular involvement, their clinical relevance in terms of immediate cardiovascular events may be uncertain. However, the use of CCTA was pivotal in this cohort, as it allows for the detection of both calcified and non-calcified plaques. This is particularly relevant in young individuals, where early coronary atherosclerosis can occur even in the presence of low or zero coronary artery calcium (CAC) scores [24]. For this reason, we considered direct plaque detection a more sensitive marker of subclinical coronary disease than CAC burden alone, which was generally low in our population. Nevertheless, it is noteworthy that the risk estimates provided by T1D-specific scores maintained a significant association with the CAC score, when categorized by the presence of any calcification (CAC > 0). Another limitation is that detailed characterization of high-risk plaque features at CCTA (such as low-attenuation plaque, positive remodelling, or the napkin-ring sign) was not included among the prespecified imaging endpoints of the current analysis. These features may provide additional insight into plaque

vulnerability in individuals with type 1 diabetes and will be explored in future work.

Third, although the combined endpoint of coronary and/or carotid disease increases sensitivity for detecting systemic atherosclerosis, biological differences between these vascular beds should be acknowledged when interpreting the results. Moreover, the relatively high prevalence of subclinical disease may partly reflect referral bias related to recruitment at a specialised cardiology centre.

Continuous risk prediction models inherently provide greater granularity than categorical risk classifications. Part of the difference in discrimination observed between the continuous engines (ST1RE and Scottish-Swedish) and the ESC categories may therefore reflect statistical properties related to information loss following categorization. For this reason, the comparison between these approaches should be interpreted accordingly. However, when ST1RE and the Scottish-Swedish model were analysed as ordinal categorical variables, their association with the imaging endpoints remained statistically significant, suggesting that their better performance is not explained solely by their continuous scale but also by their T1D-specific calibration.

Finally, and more importantly, the cross-sectional design does not allow causal inferences or the assessment of the prognostic value of imaging findings for future cardiovascular events.

Despite these limitations, both the ST1RE and Scottish-Swedish risk scores have proven reliable in distinguishing patients with early-stage atherosclerosis from those without coronary or carotid atherosclerosis. Once properly calibrated, risk scores designed to predict subclinical atherosclerosis could guide the diagnostic pathway aimed at identifying the disease at a very early stage in asymptomatic individuals, particularly young adults. This is particularly relevant in the T1D population, as previous evidence has shown that cardiovascular risk is often underestimated or misclassified in clinical practice [25] and given that a significant proportion of young patients with T1D have subclinical atherosclerosis. Such a tool would allow for the precise selection of candidates to be referred for second-level imaging, which would ensure that intensive treatment of risk factors is specifically targeted at those who truly need it, likely increasing patient compliance and adherence to treatment. However, prospective studies are warranted to determine whether such an imaging-based strategy improves risk reclassification, treatment allocation, or clinical outcomes.



**Conclusion**

In an Italian cohort of asymptomatic adults with T1D, the ST1RE and Scottish–Swedish models demonstrated good discriminatory ability for imaging-defined subclinical atherosclerosis. These findings suggest that T1D-specific risk models, although originally developed for hard cardiovascular events, could be used to identify patients more likely to harbour early-stage atherosclerotic disease and might help triage asymptomatic individuals who

could benefit from targeted cardiovascular imaging. However, as they were not designed to predict imaging outcomes, recalibration and prospective validation against imaging endpoint are needed before using predicted probabilities as absolute risks to inform clinical decision-making.

**Declarations**

The study protocol was approved by the Ethics Committee in Milan; all participants signed written informed consent.

De-identified data and supporting materials will be made available upon reasonable request to the Principal Investigator after study completion.

Authors declare no conflict of interest to be disclosed.

SG, CM, AG, AR, MR, and GIC contributed to the conceptualization; all authors contributed to investigational phase each providing data acquisition and collection based on their respective expertise and areas of competence; SM, NC, GP were responsible for CCTA data collection; BF and DB were responsible for carotid B-mode data collection; AG and AB provided statistical methodology and performed statistical analysis; CM and AG wrote the original draft of the manuscript; all authors, specifically GIC, MC and DB, contributed to critical review of the manuscript; SG was responsible for securing the necessary funding and provided supervision for the entire study. All authors read and approved the final manuscript.

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**Supplementary Materials**

**Supplementary Table 1.** Comprehensive CGM-derived glycaemic metrics of the study cohort.

**Supplementary Table 2.** Agreement among the different risk equations.

**Supplementary Table 3.** Performance and associations ST1RE, and Scottish-Swedish risk prediction tools with subclinical coronary and carotid atherosclerosis, after categorisation.

**Supplementary Table 4.** Performance and associations of the 2019 ESC stratification, ST1RE, and Scottish-Swedish risk prediction tool with and without Deprivation Index with subclinical coronary and carotid atherosclerosis, coronary artery calcium and composite imaging endpoints.

**Supplementary Figure 1.** Assessment of the accuracy of 2019 ESC and categorised ST1RE and Scottish-Swedish risk scores in predicting the presence of subclinical coronary and/or carotid atherosclerosis.

**Supplementary Figure 2.** Assessment of the accuracy of 2019 ESC, ST1RE, Scottish-Swedish and SCORE2-Diabetes risk scores in predicting

the presence of subclinical coronary and/or carotid atherosclerosis. The analysis is limited to n=61 participants aged between 40 and 69 included in the study.

**Supplementary Figure 3.** Calibration plots comparing predicted and observed probabilities for ST1RE and Scottish-Swedish Risk Scores.

**Abbreviations**

T1D: Type 1 diabetes mellitus

CCTA: coronary computed tomography angiography

cIMT: carotid intima-media thickness

$cIMT_{max}$: maximum carotid intima-media thickness

ESC: European Society of Cardiology

ST1RE: Steno Type 1 Risk Engine

CVD: cardiovascular disease

ROC: receiver operating characteristic

AUC: Area Under the receiver operating characteristic Curve

Q1–Q3: ($1^{st}$ - $3^{rd}$ quartile)

DI: deprivation index

CAC: Coronary Artery Calcium

CAD: Coronary artery disease

LDLc: Low-Density Lipoprotein Cholesterol

eGFR: estimated Glomerular Filtration Rate

BMI: Body Mass Index

CSII: continuous subcutaneous insulin infusion

SD: Standard Deviation

AGP: Ambulatory Glucose Profile

CGM: Continuous Glucose Monitoring