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SCORE2-diabetes for predicting coronary artery disease: a cardiac CT study in a diabetic moderate-risk region population

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Abstract

Background Current approaches to estimating the probability of coronary artery disease (CAD) in patients with type 2 diabetes mellitus (T2DM) often fail to reflect the clinical complexity of the condition, as they tend to oversimplify it by neglecting its progressive nature, variability in glycemic control, and the influence of disease duration. The SCORE2-Diabetes (SCORE2-D) model was developed to offer a more nuanced cardiovascular risk estimate by incorporating continuous variables and individualized risk factor weighting. However, its correlation with the actual presence and severity of CAD in diabetic patients remains under-investigated.

Objective This study aims to evaluate the association between SCORE2-D scores and CAD characteristics, as assessed by computed tomography coronary angiography (CCTA), in patients with T2DM and no prior coronary revascularization. Specifically, it investigates the relationship between SCORE2-D risk categories and the presence, morphology, and severity of coronary plaques.

Methods A retrospective analysis was conducted on patients aged 40–69 with T2DM, no history of atherosclerotic cardiovascular disease, and no severe target organ damage, who underwent CCTA at a tertiary care center. Clinical data, SCORE2-D values, and imaging results were collected. Patients were stratified into SCORE2-D risk categories, and coronary findings were compared across groups.

Results The study included 104 patients (mean age 60.9 years; mean SCORE2-D 12.2 ± 4.9). Higher SCORE2-D scores were significantly associated with the presence of coronary plaques. In the low–moderate risk group, calcified and non-calcified plaques were similarly distributed, while in the high–very high risk group, non-calcified (lipid-rich and mixed) plaques predominated, indicating potentially more vulnerable lesions. Proximal coronary segments, especially the left anterior descending artery, were most frequently involved. A progressive increase in plaque burden and

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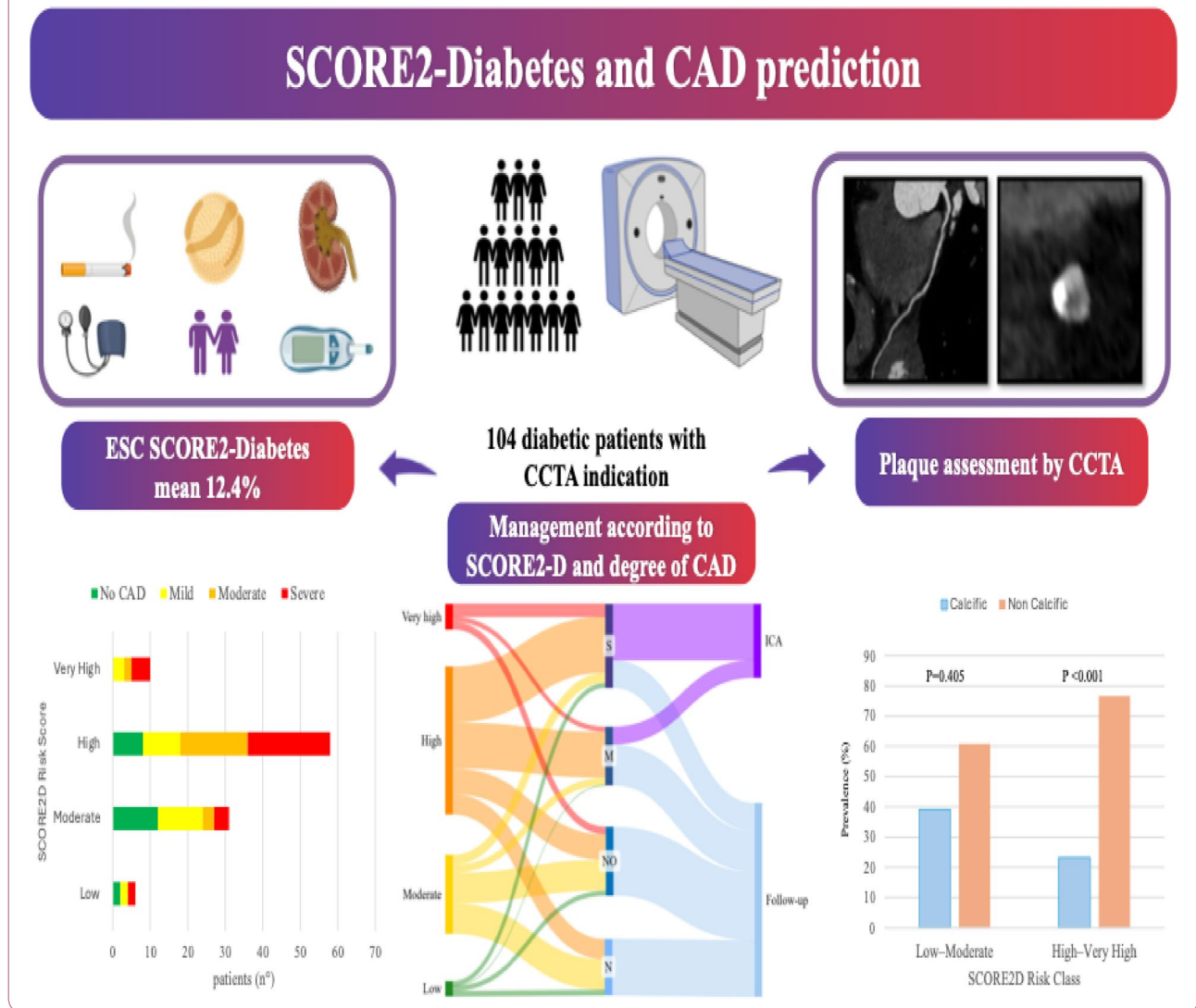
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stenosis severity was observed with rising SCORE2-D risk category. Patients at higher risk were more often referred for invasive coronary angiography.

Conclusions Higher SCORE2-D scores correlate with greater CAD burden, more severe stenosis, and a predominance of high-risk plaque features in patients with T2DM. These findings suggest that SCORE2-D may be a valuable tool in refining cardiovascular risk stratification and guiding clinical decision-making in diabetic populations.

Keywords Type 2 diabetes mellitus, SCORE2-D, Coronary CT angiography, Coronary artery disease

Graphical abstract



Introduction

Type 2 diabetes mellitus (T2DM) remains a leading cause of morbidity and mortality worldwide, primarily through its association with atherosclerotic cardiovascular disease (ASCVD) [1]. Indeed, diabetics experiencing 2–4 times higher risk of events compared to non-diabetic individuals, and this risk escalates further with worsening glycemic control [2, 3]. Contemporary guidelines recognize that not all patients with T2DM share the same

risk profile. Patients with long-standing (>10 years) T2DM or those with diabetes-related target organ damage (combined signs of nephropathy, retinopathy and neuropathy) have a cardiovascular risk approaching that of individuals with established coronary artery disease (CAD). Existing scores for baseline assessment of clinical likelihood of CAD incorporates symptoms at medical evaluation, age and number of risk factors [4, 5]. However, dynamic factors like disease duration and glycemic

status critically influence an individual diabetic patient's risk of coronary events, yet traditional CAD pre-test probability models do not fully capture these evolving characteristics [6]. Risk prediction models such as ADVANCE and DIAL have been proposed to estimate cardiovascular disease (CVD) risk in individuals with diabetes. However, their utility in European populations is limited. These models do not adequately capture the variation in CVD risk across different countries, which may lead to under- or overestimation of individual risk [7–9]. To address the need for more detailed risk assessment in diabetes, the European Society of Cardiology recently introduced the SCORE2-Diabetes (SCORE2-D) risk algorithm. SCORE2-D builds upon the conventional SCORE2 10-year cardiovascular risk model by integrating diabetes-specific variables such as age at T2DM diagnosis (duration of disease), glycated hemoglobin (a proxy for metabolic control) and estimated glomerular filtration rate (eGFR, a proxy for microangiopathy) in addition to the traditional risk factors [10]. By incorporating glycemic control and duration of disease, SCORE2-D aims to improve risk stratification for 10-year cardiovascular events in individuals with T2DM. The tool has been calibrated and validated on large cohorts, demonstrating improved discrimination for cardiovascular events compared to general-population risk models [11]. However, it is not yet known whether the SCORE2-Diabetes algorithm – beyond predicting long-term cardiovascular outcomes – can also help to estimate the pre-test probability of underlying CAD in patients with T2DM.

Although coronary computed tomography angiography (CCTA) is an effective tool for ruling out obstructive CAD in patients with low to intermediate pre-test probability according to conventional risk models, including those with diabetes [12], these models may substantially underestimate cardiovascular risk in individuals with T2DM [13, 14]. Many diabetic patients, despite being classified as low or intermediate risk by traditional clinical algorithms, harbor a high burden of cardiovascular risk when key disease-specific factors—such as long-standing hyperglycemia and prolonged T2DM duration—are taken into account. These parameters, which are often omitted in standard pre-test probability scores, are strongly associated with the presence and progression of subclinical atherosclerosis and long-term cardiovascular events [3]. Consequently, in this subset of diabetic patients, the likelihood of significant, obstructive CAD may be higher than expected, and they may derive greater diagnostic and prognostic value from an initial functional assessment (e.g., stress imaging) rather than an anatomical test. However, in addition to the degree and distribution of coronary stenosis, CCTA provides information regarding the characteristics and composition of the atherosclerotic plaque, features that have been

shown to impact cardiovascular endpoints such as non-fatal infarction and death [15].

We hypothesized that the SCORE2-D assessment—although designed for 10-year event prediction—might identify the presence and extent of CAD on CCTA in T2DM patients.

Rationale

Given that SCORE2-D accounts for disease duration, glycemic control, and renal function—key drivers of atherosclerosis—its application may align more closely with CAD burden and phenotype on CCTA than traditional scores. Uncovering such associations would support integrating SCORE2-D into clinical workflows to improve patient selection for advanced diagnostic imaging and tailor preventive/treatment strategies.

Materials and methods

We conducted a retrospective analysis of patients with T2DM who were referred for CCTA due to symptoms or clinical scenarios suggestive of stable CAD from June 2023 to December 2024 in a single center Tertiary Care Hospital. All patients included had clinical indications for CCTA based on current guidelines for the evaluation of stable chest pain or equivalent symptoms [4]. Key inclusion criteria were age 40–69 years, established T2DM, and no prior history of ASCVD. We excluded individuals with history of previous myocardial infarction, percutaneous coronary intervention, coronary bypass surgery or documented coronary plaques by a previous invasive or non-invasive angiography.

The study was approved by a local ethics committee and conducted in compliance with the principles of the Declaration of Helsinki.

Written informed consent was collected from all patients at the time of coronary computed tomography angiography.

Coronary CT angiography

CCTA was performed using a dual source high pitch CT scanner (SOMATOM Definition Force, Siemens Healthineers, Germany). Patients were prepared with beta-blockers and sublingual nitroglycerin as needed to achieve optimal heart rate control and coronary vasodilation for imaging. Scans were acquired with ECG gating and dose modulation, with typical parameters of Kvp and mA automatically adjusted for body habitus (CARE dose). CT analysis of the coronary arteries, morphological assessment, and quantification of stenosis were performed by radiologists and cardiologists with extensive experience. The degree of stenosis was determined by comparing the area of the stenotic segment with an upstream and downstream segment free of atheroma. Coronary stenoses were classified based

on the percentage of luminal area reduction on coronary as follows: mild stenosis was defined as < 50% area reduction, moderate stenosis as 50–70%, and severe stenosis as > 70%. Plaque analysis was performed manually by two experienced readers using Syngo.Via (Siemens Healthineers, Erlangen, Germany). A third independent reader repeated the analysis on a subset of cases to assess interobserver reproducibility. Fibrolipidic tissue was identified based on plaque component density. A density below 125 HU was considered fibrolipidic tissue, while above 125 HU was considered calcific tissue. Calcified plaques were defined as those where the calcific component made up at least 60% of the atheroma. If the calcific tissue component was less than 50% the plaque was defined as non-calcific plaque. Plaque with equal calcific and fibrolipidic component was considered as mixed.

SCORE2-diabetes

The variables required to calculate the SCORE2-D risk score were extracted from the patients electronic medical records. Specifically, we collected clinical and laboratory data documented within a ± 90 -days of the CCTA exam date. These data—obtained from standardized diagnostic reports archived in each patient's electronic health record—included glycated hemoglobin (HbA1c), serum creatinine (for eGFR estimation), lipid profile, blood pressure, smoking status, and age at diabetes diagnosis. The SCORE2-D 10-year cardiovascular risk percentage was then retrospectively calculated for each patient based on these parameters. From the patient's electronic medical record, it was also assessed whether the patient had undergone any additional functional diagnostic tests or coronary angiography and percutaneous or surgical revascularization post CCTA.

Statistical analysis

Continuous variables are presented as mean \pm standard deviation (SD) or median (interquartile range), depending on distribution. Categorical variables are shown as frequencies and percentages. Comparative differences across SCORE2-D risk categories (low, moderate, high, very high) were assessed using ANOVA or

Table 1 Baseline population characteristics

Variable	Value
Age, years, mean, \pm SD	60.7 \pm 5.8
Female, n (%)	33 (31.%)
Systolic blood pressure, mmHg, mean \pm SD	135.8 \pm 15.6
Hb1Ac, %, mean \pm SD	7.1 \pm 1.1
Diabetes duration, years, mean \pm SD; (median [IQR])	8 \pm 9; [5 (2–11)]
Total cholesterol, mg/dl, mean \pm SD	159 \pm 49
HDL, mg/dl, mean, \pm SD	48 \pm 13
Active smokers, n (%)	14 (13%)
TOD, n (%)	6 (5.7%)
eGFR, ml/min, mean, \pm SD	84.2 \pm 20.6
SCORE 2 Diabetes (median [IQR])	12.5 [5.3] \pm 4.9
Low risk, n (%)	6 (6%)
Moderate risk, n (%)	31 (30%)
High risk, n (%)	57 (54%)
Very high risk, n (%)	10 (10%)

eGFR estimated glomerular filtration rate; HbA1c glycated hemoglobin; HDL high density lipoprotein; IQR interquartile range; SD standard deviation; TOD target organ damage

Kruskal–Wallis tests for continuous variables and chi-squared tests for categorical data. Associations between SCORE2-D and plaque presence, composition, and stenosis severity were evaluated using Spearman's correlation and ordinal logistic regression. A two-sided p -value < 0.05 was considered statistically significant. Analyses were performed using SPSS v27.

Results

A total of 104 patients (mean age 60.7 \pm 5.8 years; 69% male) without prior revascularization were included. Mean HbA1c was 7.1 \pm 1.1% (55 mmol/mol), T2DM duration averaged 8 \pm 9 years, and eGFR was 84.2 \pm 20.6 mL/min. Active smoking was reported in 53%, and TOD was documented in 6%. Mean SCORE2-D score was 12.2 \pm 4.9, with distribution: low risk 6 (6%), moderate 31 (30%), high 58 (54%), and very high 10 (10%) (Tables 1 and 2).

Symptom distribution varied across SCORE2D risk categories. Atypical symptoms were the most frequent overall (34%), followed by absence of symptoms (34%) and dyspnea (18%). Asymptomatic presentation was

Table 2 Clinical characteristics across different risk classes

Parameter	Low risk	Moderate risk	High risk	Very high risk	p -value
Systolic blood pressure, mmHg, mean \pm SD	112.5 \pm 9.6	134.3 \pm 11.2	134.5 \pm 16.2	152.1 \pm 22.5	< 0.0011
Total cholesterol, mg/dl, mean, \pm SD	153.5 \pm 21.1	165.8 \pm 60.1	152.8 \pm 43.8	161.2 \pm 60.3	ns
HDL cholesterol, mg/dl, mean, \pm SD	54.2 \pm 15.9	51.1 \pm 15.0	45.0 \pm 12.1	50.2 \pm 11.6	ns
HbA1c mmol/mol, mean \pm SD	55.1 \pm 8.8	49.2 \pm 9.0	55.0 \pm 12.8	57.1 \pm 14.5	ns
HbA1c, %, mean \pm SD	7.2 \pm 0.8	6.7 \pm 0.8	7.2 \pm 1.2	7.4 \pm 1.3	ns
eGFR, mL/min/1.73 m ² , mean \pm SD	107.2 \pm 17.9	88.8 \pm 14.9	85.6 \pm 17.4	68.2 \pm 38.1	ns
Diabetes duration, years, mean \pm SD	2.2 \pm 2.1	5.1 \pm 4.9	8.1 \pm 8.2	23.2 \pm 12.3	< 0.0001
Active smokers, n (%)	5 (12.5%)	8 (20.5%)	15 (31%)	3 (25%)	ns

eGFR estimated glomerular filtration rate; HbA1c glycated hemoglobin; HDL high density lipoprotein; SD standard deviation; ns non significant

Table 3 Plaque presence and composition across different risk classes

Calcific plaque, n	1	7	11	3	22
No CAD, n	2	12	8	0	22
Non-calcific plaque, n	3	12	38	7	61
Total	6	31	57	10	104

CAD coronary artery disease

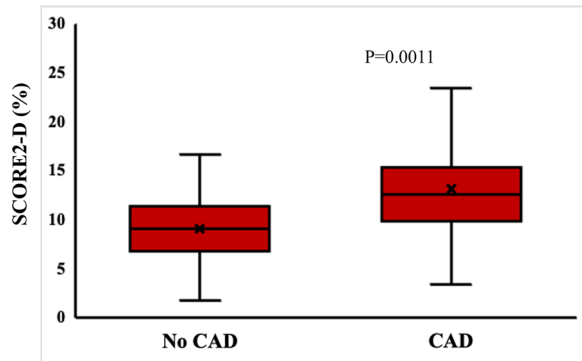


Fig. 1 SCORE2-Diabetes values according to the presence or absence of coronary artery disease (CAD). *note CAD was defined as the presence of any coronary atherosclerotic plaque, regardless of stenosis severity. CAD coronary artery disease

common even among high-risk patients (30%) (Supplementary Fig. 1).

Metformin was the most frequently prescribed drug (70%), followed by statins (59%), aspirin (45%), and beta-blockers (42%). SGLT2 inhibitors and GLP-1 receptor agonists were used in 20% and 24% of patients, respectively.

Coronary plaques were detected in 83 patients (79%). Among them, the distribution by plaque type was: mixed plaques in 37.3%, lipid-rich plaques in 36.1%, and calcified plaques in 26.5%. The severity of coronary stenosis

was distributed as follows: no detectable CAD in 21.0%, mild stenosis in 25.7%, moderate stenosis in 21.9%, and severe stenosis in 31.4% of patients (Table 3).

Patients with coronary plaques exhibited significantly higher SCORE2-D values compared to those without plaques ($13.4 \pm 6.3\%$ vs. $9.0 \pm 3.7\%$; $p < 0.01$) (Fig. 1). SCORE2-D values increased progressively with stenosis severity: $9.0 \pm 3.7\%$ in patients with no CAD, $13.0 \pm 9.1\%$ with mild stenosis, $13.0 \pm 3.8\%$ with moderate stenosis, and $14.1 \pm 4.7\%$ with severe stenosis ($p = 0.001$) (Fig. 2).

Across therapies, most treated patients presented with significant coronary stenosis ($\geq 50\%$), although the relative distribution varied numerically between drug classes (Supplementary Fig. 2). Each patient was classified according to the phenotype of the most significant coronary lesion, defined as the plaque associated with the highest degree of stenosis; accordingly, patients were categorized as having either a calcified or a non-calcified plaque phenotype. Medical therapy patterns were broadly similar between groups, although patients with calcified plaques showed a numerically higher use of metformin (78% vs. 53%) and SGLT2 inhibitors (26% vs. 9%). No statistically significant differences were observed (Supplementary Table 1). When stratifying patients by SCORE2-D risk categories, no significant difference in the distribution of calcified versus non-calcified plaques (combined soft and mixed) was observed in the low-moderate risk group ($p = 0.405$). In contrast, within the high-very high risk group, non-calcified plaques were significantly more frequent than calcified ones ($p < 0.001$). This suggests a progressive increase in the incidence of non-calcified, potentially more vulnerable plaque phenotypes with increasing cardiovascular risk (Fig. 3).

The anatomical distribution of CAD varied notably according to SCORE2-D risk stratification. In the overall

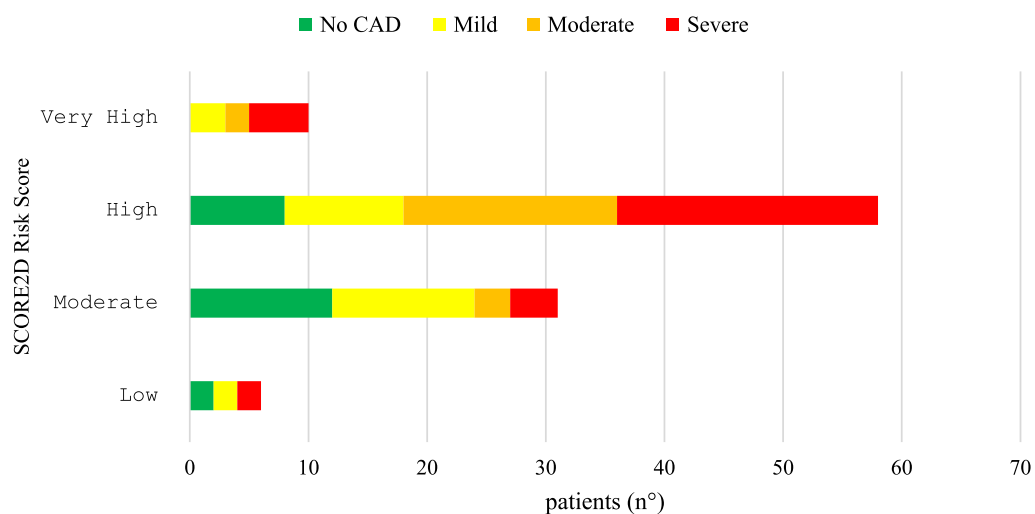


Fig. 2 Distribution of stenosis degree by SCORE2 diabetes risk class. Stenosis severity was classified according to the degree of luminal area reduction on CCTA as follows: $< 1\%$ (no CAD), $1-49\%$ (mild), $50-70\%$ (moderate), and $> 70\%$ (severe). CAD coronary artery disease

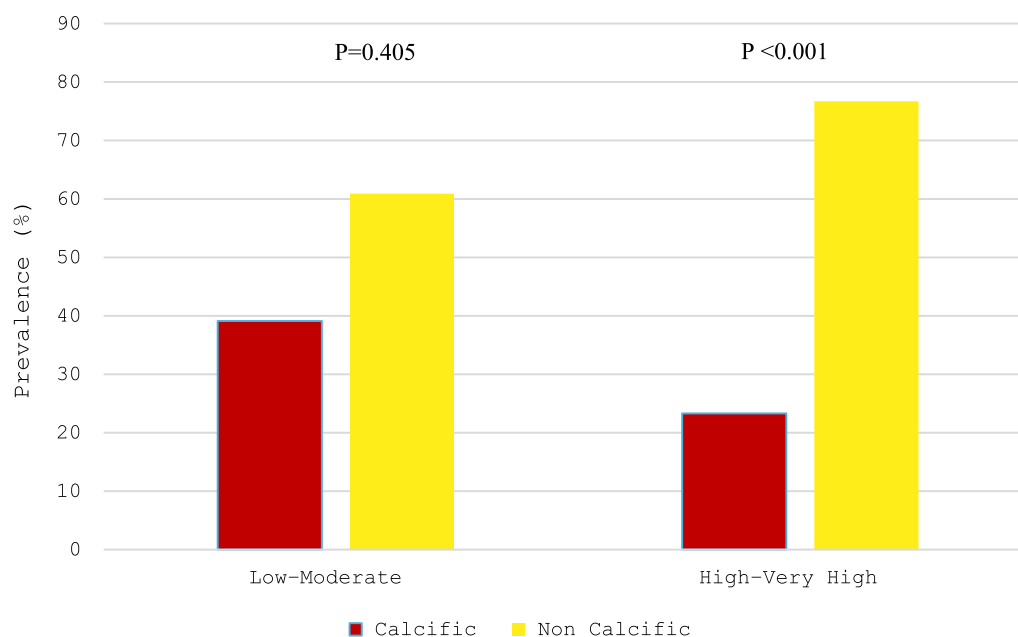


Fig. 3 Prevalence of calcific versus non-calcific plaques across SCORE2-D risk categories

cohort, stenoses were most frequently observed in the proximal and mid segments of the left anterior descending (LAD) artery, as well as in the right coronary artery (RCA) and its branches. When stratifying patients by cardiovascular risk, those in the high and very high SCORE2-D risk categories exhibited a broader and more diffuse distribution of stenoses across multiple coronary territories, particularly involving the proximal LAD and proximal RCA. Conversely, in patients classified as low or moderate risk, coronary involvement was more limited and predominantly confined to the proximal LAD, with very low prevalence in other segments. These findings suggest a clear gradient of disease burden, with increasing anatomical complexity and extent of CAD corresponding to higher SCORE2-D risk classes (Fig. 4). Left main (LM) involvement increased progressively with higher SCORE2-D risk categories, reaching its greatest prevalence in patients classified at very high cardiovascular risk (Supplementary Table 2).

Furthermore, based on SCORE2-D risk stratification, clinical management strategies differed accordingly: patients with high or very high SCORE2-D values were more frequently referred to invasive coronary angiography, whereas those at lower risk were typically managed conservatively with medical therapy, clinical follow-up, or non-invasive functional testing (40.3% vs 5.6%; $p=0.00045$) (Fig. 5).

Discussion

This study shows a significant association between SCORE2-D values and the presence of coronary plaques, the severity of stenosis, and plaque type on CCTA. By

including variables like glycemic exposure, kidney function, and age at T2DM onset, SCORE2-D shows alignment with the anatomical and pathological features of CAD compared to traditional risk models.

People with T2DM have a two- to four-times higher risk of developing cardiovascular disease over their lifetime. This includes various conditions such as CAD, stroke, heart failure, atrial fibrillation, and peripheral artery disease [16–18]. In patients with T2DM, the development of cardiovascular disease is often more multifaceted. Along with traditional risk factors, T2DM introduces additional mechanisms—such as elevated blood sugar, insulin resistance with excess insulin levels, chronic low-grade inflammation, and microvascular damage—that can further raise the risk of developing coronary heart disease [19]. However, most of the currently validated models for assessing the risk of obstructive CAD do not take these variables into account and overlook important factors such as the patient's glycemic control and the duration of T2DM, both of which have been shown to have a major impact on cardiovascular risk [20]. In clinical practice, CAD remains the main cause of illness and death in this population. Moreover, T2DM not only increases cardiovascular risk but also influences management decisions, including whether or not to perform cardiovascular imaging tests [21]. Large randomized trials did not show that routine screening with cardiovascular imaging tests reduces major cardiovascular events in asymptomatic diabetic patients [22, 23]. However, these findings are influenced by the characteristics of the study population, which consisted of asymptomatic individuals with virtually no prior cardiovascular risk stratification. For this reason, current guidelines recommend

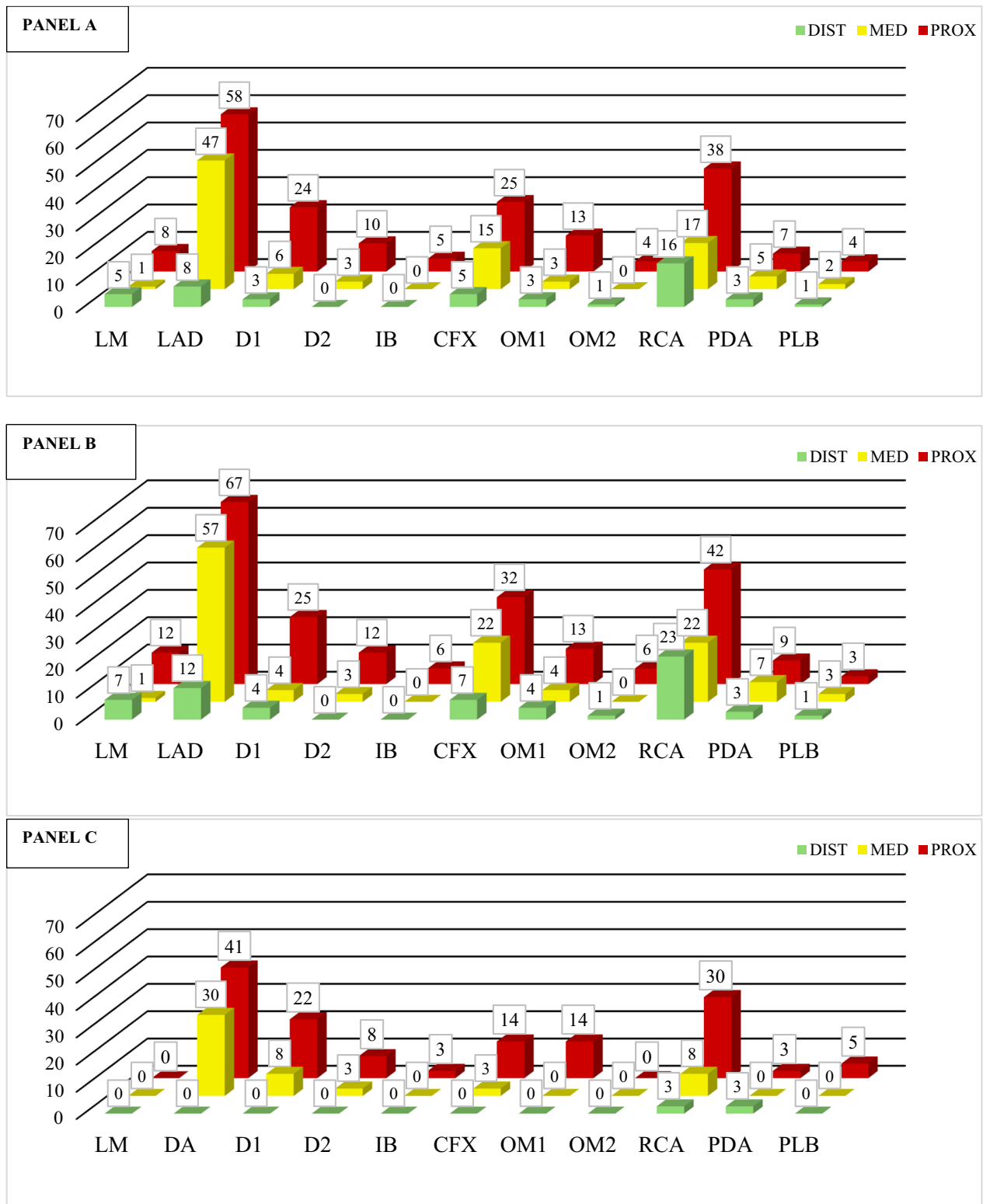


Fig. 4 Distribution and prevalence of coronary artery disease across SCORE2-Diabetes risk categories. Panel A: entire study population; Panel B: highly high SCORE2-D risk group; Panel C: low-moderate SCORE2-D risk group. LM left main; LAD left anterior descending artery; D1 first diagonal branch; D2 second diagonal branch; IB intermediate branch (Ramus Intermedius); CFX left circumflex artery; OM1 first obtuse marginal branch; OM2 second obtuse marginal branch; RCA right coronary artery; PDA posterior descending artery; PLB posterolateral branch; PROX proximal segment; MED medium segment; DIST distal segment

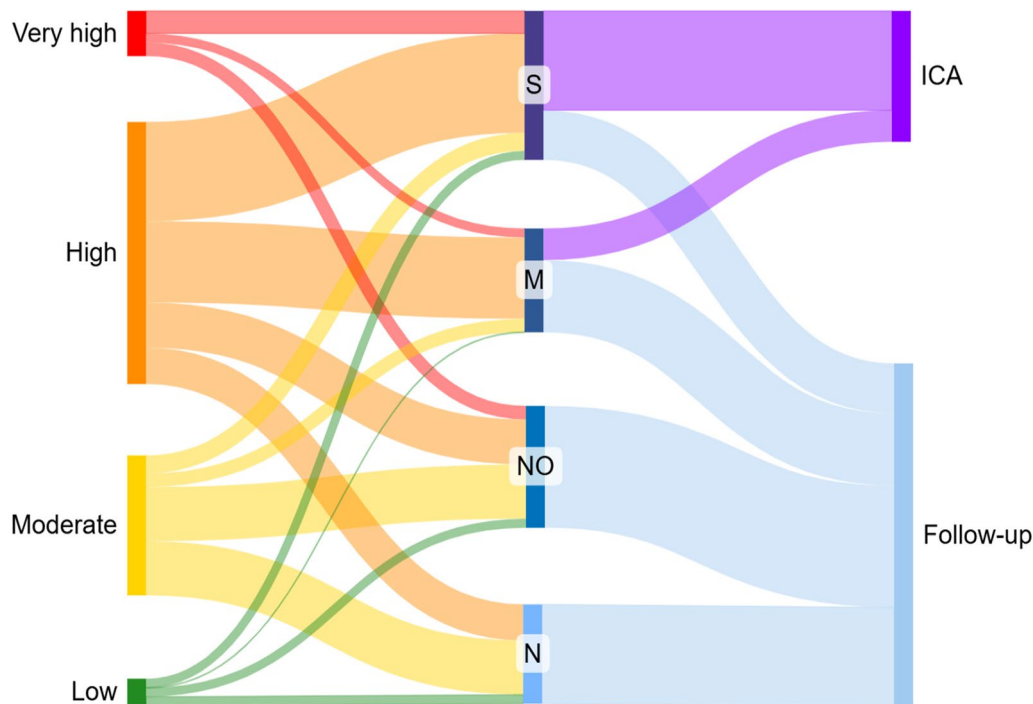


Fig. 5 Relationship between SCORE 2D and clinical approach based on CCTA results. ICA invasive coronary angiography; N No CAD; NO Non-Obstructive CAD; M moderate stenosis; S severe stenosis

a more selective approach, based on estimating pre-test probability, to decide who might benefit most from further imaging.

To our knowledge, this is the first study to demonstrate the association between SCORE2-Diabetes and the presence and extent of coronary artery disease (CAD) in a population of diabetic patients referred for CCTA.

In this context, our results suggest that SCORE2-D, thanks to its inclusion of diabetes-specific variables, may help improve cardiovascular risk estimation and better identify which diabetic patients could benefit from coronary imaging.

We observed that patients with higher scores not only had more plaques and more severe stenosis but also exhibited a greater proportion of non-calcific plaques (lipid-rich and mixed), which are considered more vulnerable and prone to acute events [24, 25]. Emerging evidence suggests that integrating stenosis severity with plaque morphology provides incremental diagnostic and prognostic value.

Recent studies have shown that combining degree of stenosis with vessel-specific plaque features significantly improves the prediction of vessel-specific ischemia compared with stenosis assessment alone, potentially refining patient selection for invasive angiography [26].

Moreover, plaque anatomy and morphology derived from CCTA may help identify patients more suitable for percutaneous coronary intervention [27]. In this context, our findings are consistent with these observations:

patients with higher SCORE2-Diabetes values exhibited more extensive and morphologically complex disease.

Together, these results underline the complementary role of SCORE2-Diabetes and CCTA plaque characterization in refining cardiovascular risk stratification and guiding personalized diagnostic and therapeutic strategies in diabetic patients. These data may be useful for defining a more appropriate and tailored diagnostic-therapeutic strategy for each individual patient, helping to identify those who require a more intensive treatment approach and closer follow-up.

Interestingly, our findings are in line with those reported by a recent study conducted by Truong et al. [28], who found a significant association between higher SCORE2-Diabetes categories and increased coronary artery calcium burden on CCTA. However, while their analysis focused exclusively on calcium score, our study provides a more comprehensive anatomical evaluation, demonstrating that higher SCORE2-Diabetes values are associated not only with greater calcific burden but also with more extensive and severe obstructive CAD, including left main and three-vessel involvement.

This broader perspective reinforces the potential clinical utility of SCORE2-Diabetes as an integrated marker of coronary atherosclerosis in diabetic patients.

Furthermore, another relevant observation concerns the subsequent diagnostic pathway of the study population. Most of the patients who underwent invasive coronary angiography, based on CT findings or

intermediate functional test results, were individuals with high SCORE2-D values, further supporting the role of this score in identifying those at highest risk who may benefit from additional testing and closer management.

Finally, an interesting finding concerns the distribution of CAD according to SCORE2-D levels. Patients with higher SCORE2-D values showed a greater incidence of multivessel involvement, including a higher prevalence of disease in more distal coronary segments. This observation is particularly relevant when considering the choice of the most appropriate diagnostic test, since CCTA, if not performed with the most advanced scanners, may have limitations in accurately assessing the true extent of CAD, especially in calcific disease and more distal segments [29].

In the diabetic population, SCORE2-D may be considered as an additional tool to complement currently validated screening strategies for cardiovascular risk assessment. By capturing the anatomical burden of coronary atherosclerosis, SCORE2-D could help stratify patients in a more detailed and individualized manner, potentially supporting a more tailored diagnostic approach. In this context, SCORE2-D may assist clinicians in identifying individuals who could benefit from further non-invasive imaging or earlier therapeutic optimization, while lower-risk patients may be appropriately managed with conservative strategies. However, prospective studies with larger cohorts are required to confirm the clinical utility of SCORE2-D as a decision-support tool in this setting.

Limitations

This study has limitations. It is a retrospective, single-center study with a relatively small sample size, so its generalizability is limited. In particular, extrapolation to broader or non-European diabetic populations should be made with caution, given regional differences in cardiovascular risk profiles and management practices. Moreover, we did not collect longitudinal outcome data, so our conclusions are based only on anatomical findings. Furthermore, the study population consists of diabetic patients with an indication for CCTA, and therefore patients with at most low-to-moderate pre-test probability, with evaluations often carried out at other centers as well. Consequently, a more accurate clinical stratification of patients, especially based on symptom assessment, would be ideal. Additionally, a potential limitation is the presence of referral bias, as diabetic patients with severely reduced renal function (eGFR < 30 mL/min/1.73 m²) were less likely to be referred for CCTA due to contrast-related concerns. In such cases, alternative non-contrast imaging tests may have been preferred, possibly leading to an underrepresentation of high-risk patients with advanced kidney disease. Finally, plaque characterization was not performed using dedicated software for component quantification, but rather through

manual quantitative analysis of each segment affected by atherosclerosis. Further research with larger, multi-center cohorts and prospective follow-up is needed to understand whether SCORE2-D-based strategies can truly improve outcomes and be cost-effective in clinical practice.

Conclusions

In patients with type 2 diabetes mellitus (T2DM) without prior revascularization, the SCORE2-D score was significantly associated with coronary plaque presence, stenosis severity, and plaque phenotype as assessed by CCTA. These findings suggest that SCORE2-D reflects underlying atherosclerotic burden and may contribute to improved cardiovascular risk assessment. Prospective studies are required to confirm these associations and to determine their relevance for clinical decision-making and outcomes.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12933-025-03000-3>.

Supplementary Material 1.

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Author contributions

R.M. Conceptualization, Writing—original draft, review & editing. M.F. Conceptualization & review M.A. and M.N. review & editing, prepared figures. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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