Cardiovascular Diabetology

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Cardiovascular risk profile in subjects with diabetes: Is SCORE2-Diabetes reliable?

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Abstract

Background People living with type 2 diabetes (T2D) are at a two- to four-fold higher risk of developing cardiovascular disease (CVD) compared with those without T2D, making early assessment of their CV risk essential. European Society of Cardiology (ESC) has developed a new model to estimate 10-year CV risk in people with T2D aged ≥ 40 years: SCORE2-Diabetes. Despite its advantages, several aspects remain to be clarified. This study evaluated the association between CV risk stratified by SCORE2-Diabetes and early CV damage assessed through arterial stiffness, intima-media thickness (IMT), and carotid atherosclerosis. Additionally, it examined the agreement between risk stratification by SCORE2 and SCORE2-Diabetes and their concordance with vascular damage.

Methods Pulse wave velocity (PWV), IMT, and carotid atherosclerosis were assessed in 179 individuals with T2D aged 40–69 years, categorized into SCORE2-Diabetes risk groups: Low ($n=20$), Moderate ($n=29$), High ($n=44$), and very high ($n=37$). Patients with a history of atherosclerotic cardiovascular disease (ASCVD) or severe target organ damage (TOD) constituted another group (ASCVD/TOD, $n=49$).

Results PWV was significantly increased from Low to very high and ASCVD/TOD groups (7.2 ± 1.1, 8.7 ± 1.9, 9.8 ± 2.3, 12.8 ± 5.1 and 11.5 ± 3.8 m/s, respectively). Similarly, IMT showed a stepwise increase with risk class (0.68 ± 0.11, 0.78 ± 0.13, 0.83 ± 0.12, 0.86 ± 0.19 and 0.87 ± 0.15 mm, respectively). Patients in very high or ASCVD/TOD group showed a higher prevalence of carotid atherosclerosis than other groups (0%, 17.24%, 11.40%, 37.83% and 40.81%, respectively). No significant differences were found between the very high and ASCVD/TOD groups in any parameter. The correlation between PWV values and increasing CV risk was stronger for SCORE2-Diabetes than for SCORE2. ROC curve analysis showed SCORE2-Diabetes had superior predictive performance for carotid atherosclerosis and high PWV compared to SCORE2 ($p=0.048$).

Conclusions Higher PWV, IMT, and carotid atherosclerosis prevalence were associated with increasing CV risk stratified by SCORE2-Diabetes, with no significant differences between the very high and ASCVD/TOD groups. SCORE2-Diabetes demonstrated a better identification of preclinical vascular damage compared to SCORE2, supporting its use as a reliable tool for identifying vascular damage in T2D patients without ASCVD or TOD.

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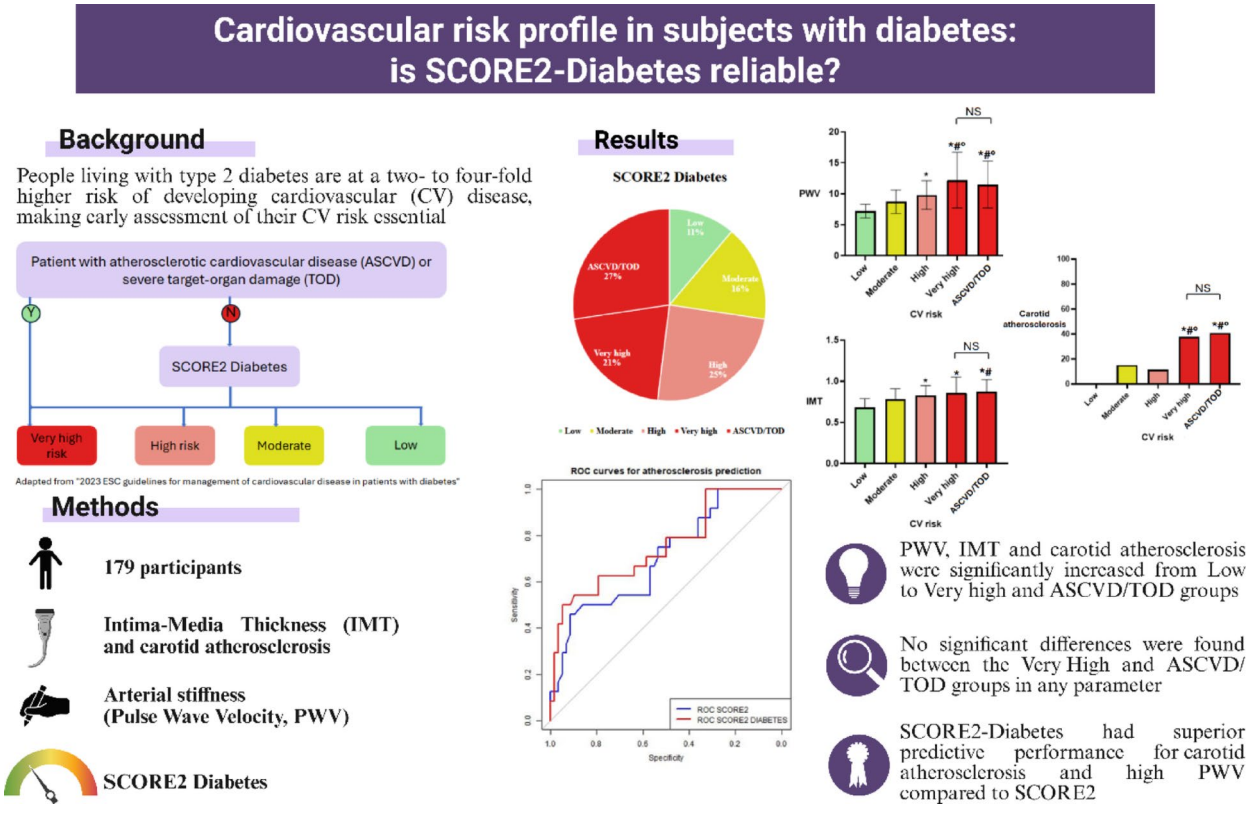
Keywords Type 2 diabetes, Cardiovascular risk, Arterial stiffness, SCORE2-Diabetes, Intima-media thickness, Atherosclerosis

Graphical abstract



Research insights

What is currently known about this topic?

- People living with type 2 diabetes (T2D) are at a higher risk of developing cardiovascular disease (CVD) compared with those without T2D. ESC has developed a new model to estimate 10-year CV risk in people with T2D, SCORE2-Diabetes.

What is the key research question?

- Is SCORE2 Diabetes a better classifier of very high CV risk people living with T2D than SCORE2?

What is new?

- This study demonstrate reliability of SCORE2 Diabetes in identifying subclinical vascular damage. SCORE2 Diabetes outperforms SCORE2 in CV risk discrimination in patients with T2D.

How might this study influence clincal practice?

- A better stratification of CV risk of people living with T2D could lead to more personalized treatment and prevention strategies.

Background

Cardiovascular diseases (CVD) remain a leading cause of illness and death in Europe, with around 13 million new cases reported in 2019 alone [1]. Type 2 diabetes (T2D) is a significant risk factor for CVD; people living with T2D are at a two- to four-fold higher risk of developing CVD compared with those without diabetes [2]. Given the extensive burden of T2D, an early assessment of CV in these patients is essential for better prevention and management.

To estimate individual CV risk over a 10-year period, risk prediction models were developed, such as SCORE2 [3] and SCORE2-OP [4], that were used in primary prevention of CVD in the general population; these scores typically integrate data on common CVD risk factors, including age, smoking status, systolic blood pressure, and total and HDL cholesterol in order to estimate the individual 10-year CV risk [5, 6].

However, given the substantial impact of T2D on CV risk, the need for specific risk models tailored in this population has emerged. Consequently, several published risk models have incorporated additional diabetes-related variables, such as age at diabetes diagnosis, glycated hemoglobin (HbA1c), renal function, to better account for the significant variability in risk among individuals with T2D [7, 8]. European society of Cardiology (ESC) has convened an effort to extend the SCORE2 10-year risk models, enabling use in individuals with T2D with the development and validation of SCORE2-Diabetes, a new model that estimates the 10-year risk of non-fatal myocardial infarction, stroke, or any CVD mortality in individuals with diabetes aged 40–69 years [9]. Accordingly, 2023 ESC Guidelines for the management of CV disease in patients with diabetes [10] recommended to estimate 10-year CVD risk using the SCORE2-Diabetes algorithm in patients aged ≥ 40 years with T2D without atherosclerotic CV disease (ASCVD) or severe target organ damage (TOD). Furthermore, patients with clinically established ASCVD or severe TOD should be considered at very high risk.

The SCORE2 diabetes, although regularly validated, does not originate from an entirely independent derivation study but rather from the integration and adaptation of the SCORE2. This raises questions about the ability of this new score to accurately stratify CV risk of the diabetic population and whether it could also be useful in identifying subclinical CV damage. This study aimed to evaluate the possible association between CV risk stratified with SCORE2-Diabetes and early CV damage evaluated with arterial stiffness, intima-media thickness (IMT) and presence of carotid atherosclerosis; moreover, we evaluated whether the very high-risk group, as defined by the guidelines, has a preclinical vascular profile comparable to individuals with a history of ASCVD or severe TOD. Finally, we analyzed the agreement between risk stratification by SCORE2-Diabetes and SCORE2 and their ability to identify patients with subclinical alterations in vascular function, specifically arterial stiffness and carotid atherosclerosis.

Methods

Study subjects

Persons with a previous diagnosis of T2D were enrolled from patients attending our University Hospital for diabetes and CV risk evaluation. The inclusion criterion was an age range of 40–69 years. All participants underwent a physical examination and review of their clinical history, smoking status and medications. The exclusion criteria were type 1 diabetes, malignancies, rheumatological disease, drug and alcohol abuse, and use of drugs affecting glucose metabolism. We overall enrolled 179 participants.

Study groups

Subjects were divided into five groups according to ESC guidelines [10]. Those without ASCVD or TOD underwent risk stratification using the SCORE2-Diabetes, resulting in their classification into four groups: Low, Moderate, High, and very high CV risk. Patients with a history of ASCVD or severe TOD constituted a study group (ASCVD/TOD). ASCVD was defined as clinically established atherosclerotic disease, including conditions like coronary artery disease (CAD), cerebrovascular disease, peripheral artery disease (PAD), and aortic atherosclerotic disease. Severe TOD was defined as: eGFR < 45 mL/min/1.73 m^2 irrespective of albuminuria, or eGFR 45–59 mL/min/1.73 m^2 and microalbuminuria (UACR 30–300 mg/g; stage A2), or Proteinuria (UACR > 300 mg/g; stage A3), or Presence of microvascular disease in at least three different sites (e.g. microalbuminuria (stage A2) plus retinopathy plus neuropathy).

Body mass index (BMI) was calculated as weight (kg)/[height (m)]^2. Blood pressure (BP) was measured with a calibrated sphygmomanometer after 10 min resting. Venous blood samples were drawn from the antecubital vein on the morning after an overnight fast. Baseline venous blood samples were obtained for the measurement of clinical biochemistry parameters.

Biochemical analyses

Fasting glucose, serum total cholesterol, triglycerides, and HDL cholesterol were measured using available enzymatic methods.

HbA_{1c} was measured via high performance liquid chromatography using a National Glycohemoglobin Standardization Program and was standardized to the Diabetes Control and Complications Trial (DCCT) [11] assay reference. Chromatography was performed using a certified automated analyzer (HLC-723G7 hemoglobin HPLC analyzer; Tosoh Corp.) (normal range 4.25–5.9%).

Estimated glomerular filtration rate (eGFR) was assessed with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Equation [12]. Albuminuria determination was performed as albumin-to-creatinine ratio (UACR) in a spot urine sample and the mean of two different values obtained in a period of 3–6 months was considered [13]. LDL cholesterol concentrations were estimated using the Friedewald formula.

Carotid ultrasound examination

Ultrasound scans were performed using a high-resolution B-mode ultrasound system, as previously described [14]. Briefly, all ultrasound examinations were performed by a single physician who was blinded to the clinical and laboratory characteristics of the patients. Longitudinal B-mode (60 Hz, 128 radiofrequency lines) images of the right common carotid artery 2 cm below the carotid

bulb were obtained using a high-precision echo tracking device (MyLab Alpha, Esaote, Maastricht, NL) paired with a high-resolution linear array transducer (13 MHz) to acquire IMT using the built-in echo tracking software.

IMT was measured also in the presence of carotid plaques, as per the protocol. However, in such cases, measurements were taken from the closer plaque-free arterial segments, in line with current recommendations, to ensure reliability and comparability.

Pulse wave velocity

The SphygmoCor CvMS (AtCor Medical, Sydney, Australia) system was used for the determination of the pulse wave velocity (PWV). This system uses a tonometer and two different pressure waves obtained at the common carotid artery (proximal recording site) and at the femoral artery (distal recording site). An electrocardiogram was used to determine the start of the pulse wave. The PWV was determined as the difference in travel time of the pulse wave between the two different recording sites and the heart, divided by the travel distance of the pulse waveform. The PWV was calculated on the mean basis of 10 consecutive pressure waveforms to cover a complete respiratory cycle.

Pulse wave analysis

All measurements were made from the right radial artery by applanation tonometry using a Millar tonometer (SPC-301; Millar Instruments, Houston, TX, USA). The measurements were performed by a single investigator with the subject in the supine position. The data were collected directly with a desktop computer and processed with SphygmoCorCvMS (AtCor Medical, Sydney, Australia). The aortic waveform has two systolic pressure peaks, the second is caused by wave reflection from the periphery. With arterial stiffening, both the PWV and the amplitude of the reflected wave are increased such that the reflected wave arrives earlier and adds to (or augments) the central systolic pressure. The aortic waveform in the pulse wave analysis was subjected to further analysis for the calculation of the aortic augmentation (Aug) and augmentation index (AugI, calculated by dividing augmentation by pulse pressure, that the difference between the systolic and diastolic BPs) [15].

Statistical analyses

The sample size was calculated based on PWV using a level of significance (α) set to 5% and a power (1-β) set to 80%, with an estimated difference of PWV of 15% between low and very high risk groups. The estimated sample size was 19 patients per group. Statistical comparisons of clinical and biomedical parameters were performed using Stat View 6.0 and R 4.4.1 for Windows. The data are presented as mean ± SD or median (interquartile range). The distributional characteristics of each variable, including normality, were assessed using the Kolmogorov–Smirnov test. One-way ANOVA for clinical and biological data was performed to test the differences among groups, with the Bonferroni post hoc test for multiple comparisons. The χ^2 test was used for categorical variables. A P value < 0.05 was considered significant. When necessary, numerical variables were logarithmically transformed to reduce skewness. Spearman's rank correlation was used to evaluate the association between PWV and cardiovascular risk categories, given the ordinal nature of the latter.

The subgroup of patients without evidence of ASCVD or TOD was re-stratified for CV risk using the SCORE2 algorithm [9]. The agreement between risk stratification by SCORE2 and SCORE2-Diabetes was analyzed and the concordance between ultrasound findings (carotid atherosclerosis) and the two scoring systems was assessed. Sensitivity for plaque prediction was calculated for both SCORE2 and SCORE2-Diabetes. Specificity was not determined due to the inability of a normal ultrasound to exclude Low or Moderate CV risk definitively.

Receiver operating characteristic (ROC) curve analysis was conducted to compare the performance of SCORE2 and SCORE2-Diabetes in predicting CV risk as estimated by carotid ultrasound and arterial stiffness (PWV > 9.25 m/s, the median PWV value for the population). The areas under the ROC curve (AUCs) were calculated for both scoring systems, and the De Long test was applied to evaluate statistical differences between AUCs.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Comitato Etico Catania 2, protocol n. 270/C.E. 26th April 2022. Informed consent was obtained from every participant.

Results

Study population characteristics

According to the eligibility criteria, 179 participants were included in this study. According to SCORE2-Diabetes, the study population was divided into the following five groups: Low risk group (n = 20), Moderate risk group (n = 29), High risk group (n = 44), Very high risk group (n = 37) and ASCVD/TOD group (n = 49). As shown in Table 1, mean age increased progressively across risk categories from low to very high and to ASCVD/TOD group (50.00 ± 5.44 years, 55.60 ± 3.93 years, 61.97 ± 5.33 years, 66.70 ± 2.39 years, 65.20 ± 3.67 years). The prevalence of male sex was higher in all risk categories, compared to the Low risk group (35%), reaching a male prevalence of 89.8% in the ASCVD/TOD group. Also, the proportion

Table 1 Clinical, metabolic and therapy characteristics of the study population according to CV risk class

	Low risk (*n* = 20)	Moderate risk (*n* = 29)	High risk (*n* = 44)	Very high risk (*n* = 37)	ASCVD/TOD group (*n* = 49)
Age, years	50.00 ± 5.44	55.60 ± 3.93*	61.97 ± 5.33***#**	66.70 ± 2.39***#°**	65.20 ± 3.67***#°**
Sex, no (%) of males	7 (35)	20 (69.9) *	32 (72.7) *****	29 (78.4) *****	44 (89.8) ***°**
Active smokers, no (%)	2 (10)	7 (24.13)	15 (34.09)	16 (40.5) *****	19 (38.7) *****
Age at diabetes diagnosis, years	49 ± 4.63	52 ± 6.04	51.66 ± 10.33	53.36 ± 12.46	51.33 ± 9.87
SBP, mmHg	122 ± 15	128 ± 14	135 ± 13*	133 ± 9*	134 ± 12*
Total cholesterol, mg/dl	180.45 ± 37	181 ± 39	169 ± 40	160 ± 33#	135 ± 32*#°
c-HDL, mg/dl	53.09 ± 13.17	50.9 ± 15.5	45.75 ± 9.96	45.48 ± 11.4	42.71 ± 11*#
c-LDL, mg/dl	104.39 ± 38.88	106.12 ± 38.88	93.95 ± 36.20	88.67 ± 29.73 *#	62.72 ± 26.46***#°†**
HBA1c, %	6.6 ± 0.92	6.55 ± 0.90	7.5 ± 1.5*#	6.90 ± 1.14°	7.69 ± 1.4*#
Fasting glucose, mg/dl	133 ± 52	116.55 ± 20.7	148.65 ± 52.4#	127.61 ± 40.8°	143.87 ± 45.9#
eGFR, ml/min/1.73m^2	112.35 ± 25.98	100.18 ± 13.99	87.32 ± 19.60*#	54.19 ± 16.94*#°	68.87 ± 24.48*#°
BMI, kg/m^2	31.68 ± 6.01	29.61 ± 5.74	30.04 ± 4.26	27.73 ± 3.5#	29.06 ± 4.59*
Uric acid, mg/dl	5.44 ± 1.93	4.86 ± 1.15	5.59 ± 1.31	6.13 ± 1.68***#**	4.29 ± 1.34***#°†**
SGLT2i	8 (53%)	8 (31%)	13 (34%)	10 (33%)	17 (40%)
GLP-1 RAs	5 (33%)	11 (42%)	20 (53%)	13 (43%)	15 (36%)
Statin	14 (93%)	15 (60%)	32 (84%)	21 (70%)	31 (74%)
Anti hypertensive therapy	5 (33%)	16 (62%)	21 (55%)	16 (53%)	25 (60%)
Urate lowering therapy	0 (0%)	0 (0%)	1 (2%)	3 (8%)	4 (8%)

Data are presented as mean ± SD, median (IQR), or percentage. ASCVD/TOD, atherosclerotic cardiovascular disease or severe target organ damage; SBP, systolic blood pressure; c-HDL, HDL cholesterol; c-LDL, LDL cholesterol; HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate; BMI, body mass index; SGLT2i, sodium-glucose co-transporter 2 inhibitors; GLP-1 RAs, glucagon-like peptide-1 receptor agonists. *$P < 0.05$ versus group Low; #$P < 0.05$ versus group Moderate; °$P < 0.05$ versus group High; †$P < 0.05$ versus group very high

of smokers increased from the low risk group (10%) to the very high risk (40.5%) and ASCVD/TOD groups (38.7%). Systolic blood pressure was significantly higher in all groups compared to the Low risk group. Levels of total and HDL cholesterol decreased significantly with increasing CV risk.

Regarding diabetes-specific parameters, no significant differences were observed in the age of diabetes diagnosis across groups. HbA1c was significantly higher in the High risk (7.5 ± 1.5%) and ASCVD/TOD groups (7.69 ± 1.4%) compared to the Low and Moderate risk groups (6.6 ± 0.92% and 6.55 ± 0.90%, respectively). eGFR decreased significantly with increasing CV risk: Low (112.35 ± 25.98 ml/min/1.73 m^2), Moderate (100.18 ± 13.99 ml/min/1.73 m^2), High (87.32 ± 19.60 ml/min/1.73 m^2), Very high (54.19 ± 16.94 ml/min/1.73 m^2), and ASCVD/TOD (68.87 ± 24.48 ml/min/1.73 m^2).

Regarding population characteristics not considered in the SCORE2-Diabetes model, we found that BMI was highest in the Low risk group (31.68 ± 6.01 kg/m²) and progressively decreased across higher risk categories (29.61 ± 5.74 kg/m² in the Moderate group, 30.04 ± 4.26 kg/m² in the High group, and 27.73 ± 3.5 kg/m² in the very high group). In the very high risk group, BMI was significantly lower compared to the Moderate risk group ($p = 0.01$). Similarly, in the ASCVD/TOD group, BMI was significantly lower compared to the Low risk group ($p = 0.05$). Fasting glucose levels also varied across risk categories. The highest values were observed in the High risk group and the ASCVD/TOD group, both significantly higher compared to the Moderate risk group ($p < 0.05$). Uric acid levels in the very were significantly higher in High risk group compared with Low risk and Moderate risk groups ($p = 0.05$). In the ASCVD/TOD group, uric acid levels were significantly lower compared to the Low, Moderate, and very high groups ($p < 0.0001$ vs Low, $p < 0.0001$ vs Moderate, $p = 0.01$ vs High, $p = 0.0001$ vs very high).

For none of the examined population characteristics was a statistically significant difference observed between the very high risk group and the ASCVD/TOD group.

The use of sodium-glucose co-transporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) was comparable across CV risk groups. Statin therapy and antihypertensive therapy were widely used, without statistically significant differences among groups. Urate-lowering therapy showed a gradual increase from 0% in Low and Moderate risk groups to 8% in very high and ASCVD/TOD groups.

Vascular profile of the study population according to CV risk classes

PWV significantly and progressively increased from low to very high and ASCVD/TOD groups (7.2 ± 1.1 m/s, 8.7 ± 1.9 m/s, 9.8 ± 2.3 m/s, 12.8 ± 5.1 m/s, 11.5 ± 3.8 m/s). Similar trend was observed for IMT, with significantly higher values as the risk classes increase (0.68 ± 0.11 mm, 0.78 ± 0.13 mm, 0.83 ± 0.12 mm, 0.86 ± 0.19 mm, 0.87 ± 0.15 mm). Then, patients with very high risk or belonging to ASCVD/TOD group were found to have

a higher prevalence of carotid atherosclerosis than the other groups (Low 0%, Moderate 17.24%, High 11.40%, very high 37.83%, ASCVD/TOD 40.81%) (Fig. 1).

Notably, we found no statistically significant difference in the considered parameters between the very high risk group and ASCVD/TOD group.

A positive correlation (Spearman's $R = 0.48$, $p < 0.05$) was found between PWV values and increasing CV risk categories, as shown in Fig. 2.

Reclassification of diabetic patients: from SCORE2 to SCORE2-Diabetes

Then, all the patients without ASCVD or TOD ($n = 130$) underwent a CV risk re-stratification based on the SCORE2 according to previous ESC guidelines, resulting in the following patient's distribution: Low risk group ($n = 37$), Moderate risk group ($n = 63$), High risk group ($n = 30$), and ASCVD/TOD group ($n = 49$). Comparison of risk stratification between SCORE2 and SCORE2 Diabetes is showed in Fig. 3.

Notably, among the 100 patients initially classified as low or moderate risk by SCORE2, 67 individuals (67%) were reclassified as high ($n = 37$) or very high risk ($n = 30$) when applying the SCORE2-Diabetes algorithm.

A positive correlation (Spearman's $R = 0.28$, $p < 0.05$) was found also between PWV values and increasing CV risk categories, as shown in Fig. 4, although this correlation was weaker compared to that observed with the SCORE2-Diabetes classification ($R = 0.48$, $p < 0.05$).

Sensitivity in plaque prediction: SCORE2 versus SCORE2-Diabetes

The sensitivity of SCORE2 Diabetes in predicting plaque was 58% compared to 45% for SCORE2. Specificity was not reported, as a ultrasound without evidence of atherosclerosis does not necessarily imply Low or Moderate CV risk, especially in patients with T2D; thus, its clinical interpretability in this context may be limited. Further analysis using ROC curves between the two scoring systems and presence of carotid plaque revealed an AUC of 0.706 (95% confidence interval (CI) 0.581–0.832) for SCORE2 and 0.752 (95% CI 0.631–0.874) for SCORE2 Diabetes, as shown in Fig. 5. Although the AUC for SCORE2 Diabetes is nominally higher than that for SCORE2, the De Long test for comparing AUC showed no statistically significant difference ($p = 0.13$).

Finally, ROC curve analysis between the two scoring systems and the risk classification estimated by arterial stiffness (PWV > 9.25, where 9.25 represents the median PWV value of the population) revealed an AUC of 0.706 (95% CI 0.581–0.832) for SCORE2 and 0.752 (95% CI 0.631–0.874) for SCORE2 Diabetes, as shown in Fig. 6. The De Long test for comparing AUC showed that they were statistically different ($p = 0.048$), indicating that SCORE2 Diabetes is a significantly better classifier than SCORE2.

Discussion

In this study, we investigated the association between CV risk stratified with SCORE2-Diabetes and early vascular damage evaluated with arterial stiffness, IMT and carotid atherosclerosis. Furthermore, we analyzed the agreement between risk stratification by SCORE2-Diabetes

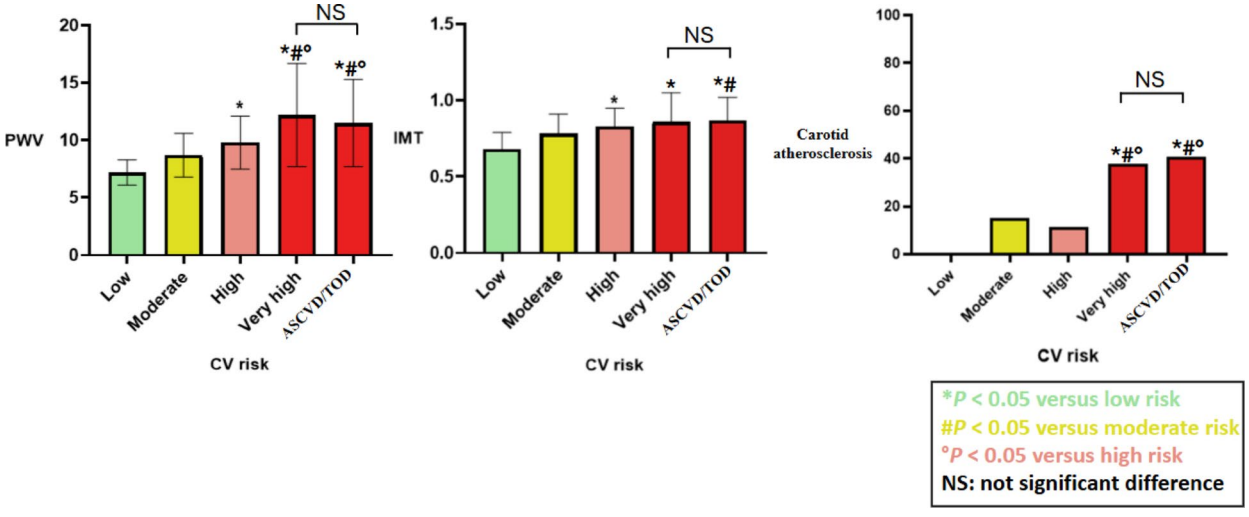


Fig. 1 Vascular profile of the study population according to CV risk classes. Box plots showing PWV significantly increased from low to very high and ASCVD/TOD groups. Similar results for IMT, with progressively higher values as the risk classes increase. No statistically significant difference was found in the considered parameters between the very high risk group and ASCVD/TOD group. *$P < 0.05$ versus low group; #$P < 0.05$ versus Moderate group; °$P < 0.05$ versus high group. NS, not significant difference

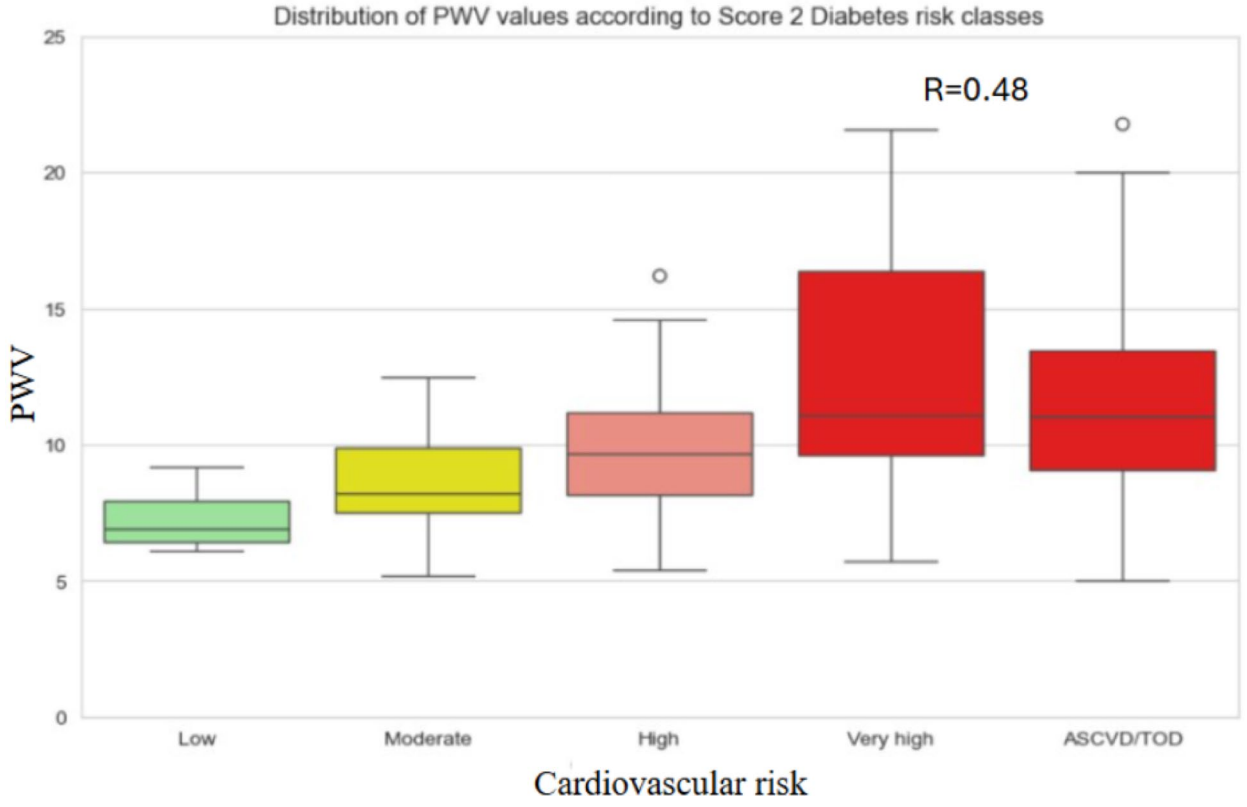


Fig. 2 PWV distribution in risk classes according to SCORE 2 Diabetes. The boxplot shows the distribution of PWV across different cardiovascular risk classes stratified according to SCORE2 Diabetes. ASCVD/TOD: atherosclerotic cardiovascular disease or severe target organ damage. Spearman's correlation ($R = 0.48$, $p < 0.05$) confirmed a positive association between PWV and increasing risk categories

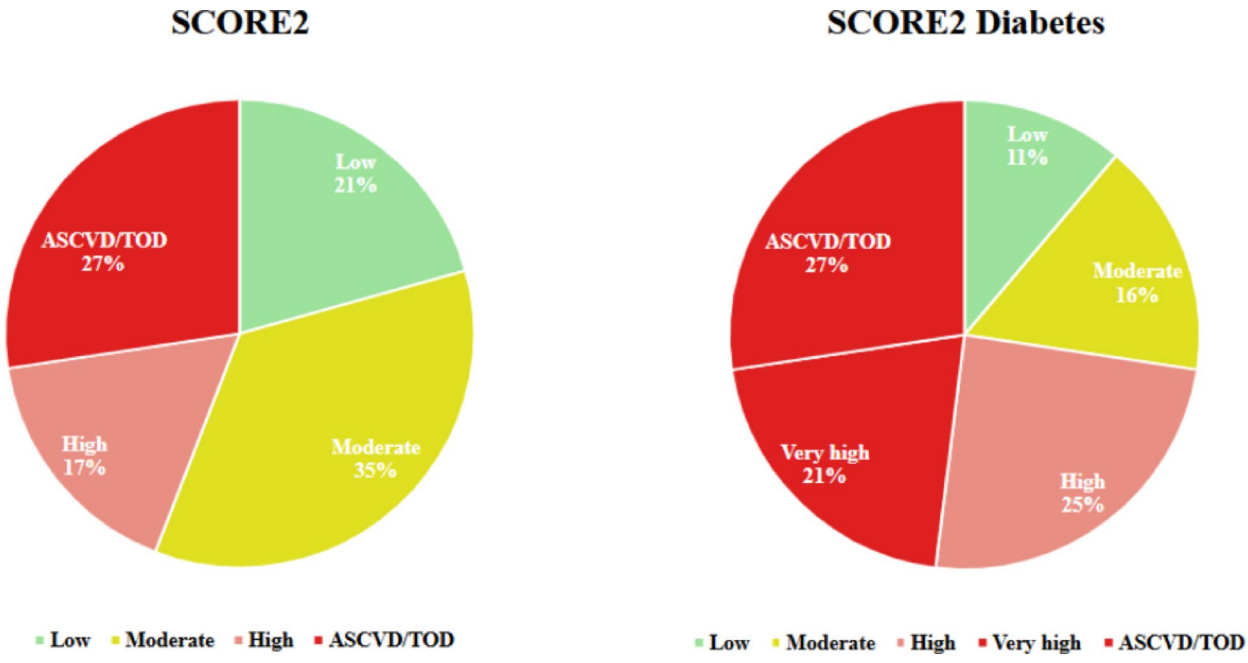


Fig. 3 Comparison of risk stratification between SCORE2 and SCORE2-Diabetes in the study population. ASCVD/TOD: atherosclerotic cardiovascular disease or severe target organ damage. Among the 100 patients initially classified as low or moderate risk by SCORE2, 67 were reclassified as high or very high risk using SCORE2-Diabetes, highlighting a significant reclassification that may impact clinical decision-making

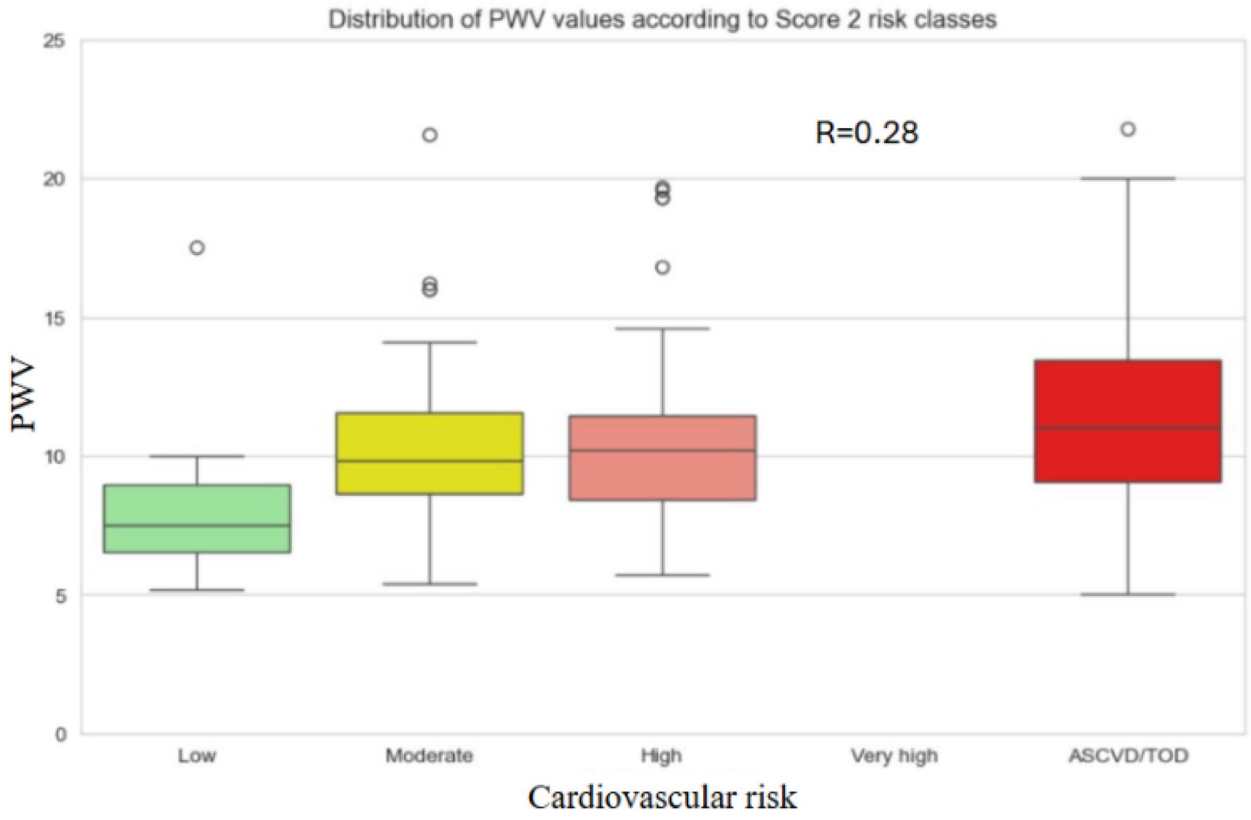


Fig. 4 The boxplot shows the distribution of PWV across different cardiovascular risk classes stratified according to SCORE2. ASCVD/TOD: atherosclerotic cardiovascular disease or severe target organ damage. Spearman's correlation ($R = 0.28$, $p < 0.05$) confirmed a positive association between PWV and increasing risk categories

and SCORE2 and their ability to identify patients with subclinical alterations in vascular function. SCORE2-Diabetes, being specifically designed for individuals with diabetes, is a potentially valuable tool that could assist clinicians in determining the intensity of certain treatments (e.g., lipid-lowering therapies) as well as in considering additional interventions to prevent CVD, such as sodium-glucose co-transporter 2 inhibitors or glucagon-like peptide-1 receptor agonists [16].

We found significantly increasing PWV values from Low to very high and ASCVD/TOD groups. Similar statistically significant results were obtained for IMT. Moreover, patients with very high risk or belonging to ASCVD/TOD group were found to have a higher prevalence of carotid atherosclerosis than the other groups. Finally, we found no statistically significant difference in the parameters considered between the very high risk group and ASCVD/TOD group.

Previous studies have investigated the efficacy of SCORE2 Diabetes in different populations to assess its relevance in demographic and socioeconomic contexts distinct from those in which the score was originally developed and validated. In a population of 26,544 diabetic individuals, SCORE2 Diabetes showed strong predictive accuracy for CV events in the Dutch population, while it underestimated event's risk for non-Dutch individuals; moreover, SCORE2 Diabetes underestimated the CV risk in groups with low socioeconomic status [17].

In this study, SCORE2 Diabetes outperforms SCORE2 in CV risk discrimination in patients with T2D: the correlation between PWV values and increasing CV risk categories according to SCORE 2, despite being statistically significant, was weaker compared with that observed with the SCORE2-Diabetes classification, thus limiting the clinical relevance of SCORE2 in T2D population. Moreover, the comparison of ROC curves of the two scoring systems for the prediction of carotid atherosclerosis and high arterial stiffness revealed a higher AUC for SCORE2 Diabetes than for SCORE2, suggesting that SCORE2 Diabetes may provide a significant but modest improvement in identifying subclinical vascular damage in this population, as reflected by its slightly higher AUC compared to SCORE2. A similar analysis was performed by Campos Fernandez et al., who demonstrated that SCORE2 outperforms SCORE in predicting carotid plaques and increased IMT in rheumatoid arthritis patients [18]. Importantly, the clinical relevance

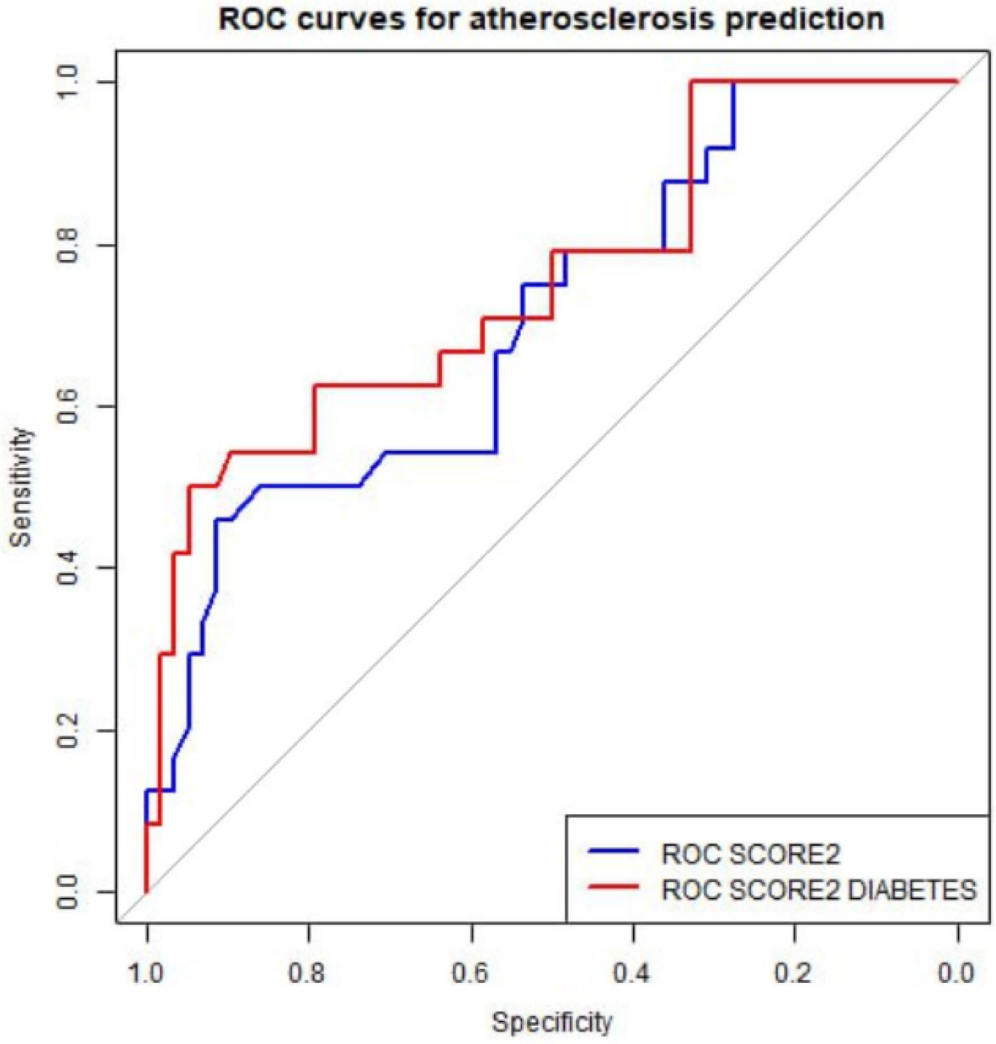


Fig. 5 ROC curves illustrate the performance of SCORE2 and SCORE2 Diabetes in predicting cardiovascular risk according to presence of carotid plaque (atherosclerosis prediction)

of adopting SCORE2-Diabetes is further underlined by the reclassification analysis: 67 out of 100 patients initially considered at Low or Moderate risk by SCORE2 were reclassified as high or very high risk using SCORE2-Diabetes. This substantial shift in risk categorization may have meaningful implications for clinical decision-making, as patients reclassified to higher risk categories would become eligible for earlier and potentially more intensive preventive interventions, such as stricter LDL cholesterol targets or antihypertensive therapy, according to current ESC guidelines.

The SCORE2-Diabetes model does not take into account certain important CV risk factors, such as obesity and BMI assessment. Interestingly, in our study population, BMI values were lower in the higher risk categories. Incorporating BMI into the score could potentially improve CV risk stratification, particularly when adjusted for age. It has been demonstrated that a high BMI has a much greater impact on younger individuals in terms of diabetes and CVD risk [19]. Moreover, it is possible that patients in the ASCVD/TOD category receive more intensive medical treatment and monitoring, leading to better dietary control and weight management. Alternatively, the lower BMI observed in the highest risk category might be partially explained by the presence of established CVD. This group may include older or more clinically fragile patients, in whom weight loss or lower BMI could reflect disease-related metabolic changes or comorbidities. Notably, recent evidence has described an "obesity paradox," where higher BMI levels, particularly in older adults, are not consistently associated with increased cardiovascular mortality, and may even appear protective in certain clinical contexts [20, 21].

Regarding uric acid, this parameter is a well-established independent CV risk factor [22] and exhibited a heterogeneous distribution across risk categories, with

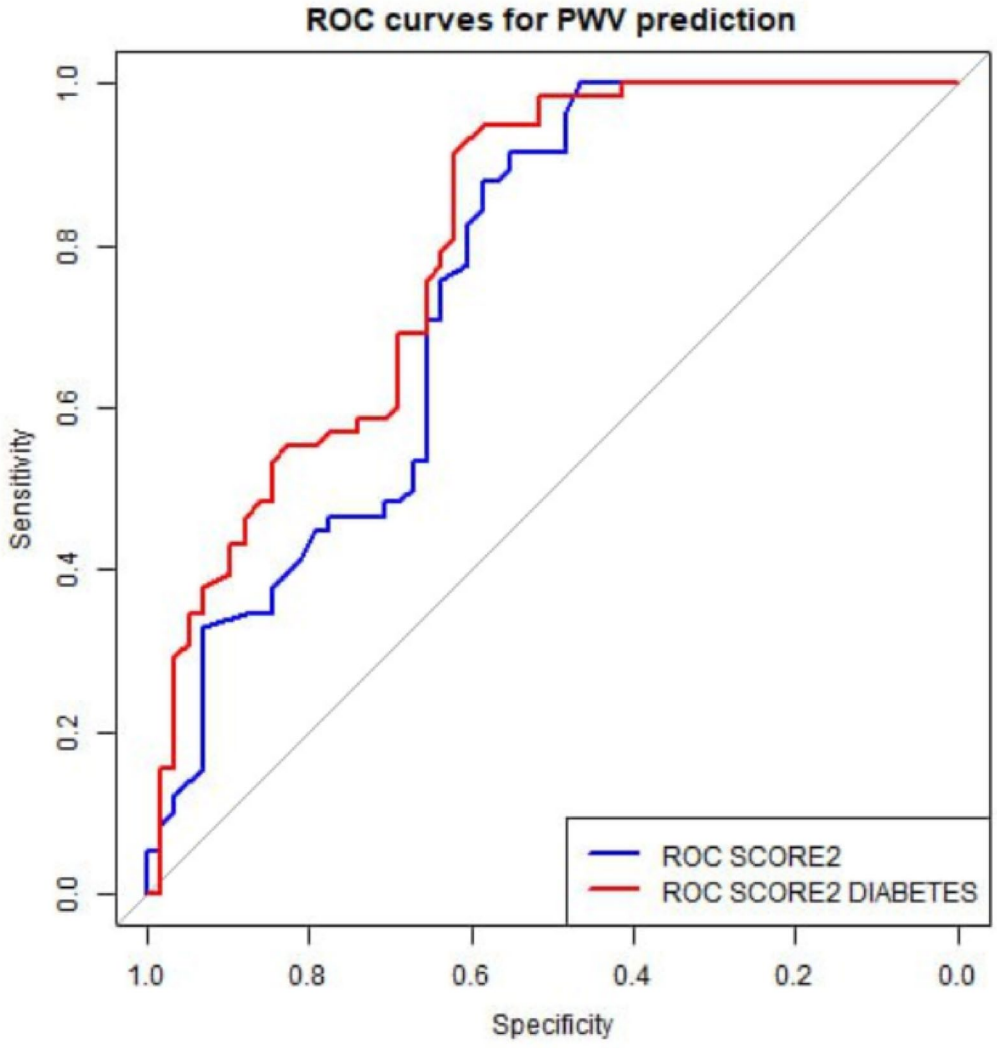


Fig. 6 ROC curves illustrate the performance of SCORE2 and SCORE2 Diabetes in predicting cardiovascular risk according to arterial stiffness results (prediction of PWV > 9.25)

increasing values from the low to very high risk groups. In the ASCVD/TOD group, uric acid levels were significantly lower compared to all other groups. This observation could also be attributed to a greater use of pharmacological interventions in these patients, as reflected by the higher prevalence of urate-lowering therapy, which increased from 0% in the Low and Moderate risk groups to 8% in the very high and ASCVD/TOD groups.

Our study presents some strengths and limitations. This is a cross-sectional study: thus, a longitudinal causal relationship cannot be established. All participants were White. Moreover, the proportion of individuals expected in the risk categories of the Italian classification (moderate-risk region) was not consistent within our study group, with a higher proportion of individuals classified as high and very high risk compared to expectations [23]. This discrepancy may be attributed to the fact that patients were enrolled in a secondary care facility managing diabetic individuals requiring more intensive hospital-based care, as well as due to the small population size, which does not clearly represent the entire diabetic population. Additionally, LDL cholesterol was estimated using the Friedewald formula, which may lead to inaccurate values in the presence of elevated triglyceride levels—a common condition in individuals with T2D—representing a potential methodological limitation. Furthermore, arterial stiffness and IMT, while non-invasive and strongly associated with CV events [24], rare surrogate markers of atherosclerosis and do not necessarily reflect CAD. Indeed, severe CAD may be present in the absence of significant alterations in other vascular districts [25, 26].

As concerns strengths, we provided a comprehensive non-invasive CV risk assessment of subjects with diabetes with IMT, arterial stiffness and carotid ultrasound. In

addition, all the subjects of the study underwent SCORE2 Diabetes algorithm in order to assess their CV risk according to ESC guidelines. Furthermore, we focused on the ability of SCORE2-Diabetes to detect subclinical vascular damage (e.g., carotid plaques), particularly in patients at very high risk, who exhibited a vascular profile comparable to that of patients with clinically established ASCVD or TOD.

Conclusions

In conclusion, we found increasing PWV and IMT in diabetic patients with progressively increasing risk classes evaluated through SCORE2-Diabetes and a higher prevalence of carotid atherosclerosis in patients of very high risk group. Moreover, patients of very high risk group had similar vascular profile than patients with established ASCVD or TOD, showing the reliability of SCORE2-Diabetes in estimating CV risk, also in term of preclinical vascular damage.

Considering our evidence, SCORE2-Diabetes could play a critical role in clinical practice for assessing CV risk in individuals with diabetes. However, it is essential to evaluate the patient comprehensively, addressing aspects not included in the score, to avoid underestimating or overestimating their risk.

Abbreviations

ASCVD	Atherosclerotic cardiovascular disease
BMI	Body mass index
CKD-EPI	Chronic kidney disease epidemiology collaboration
CV	Cardiovascular
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
FG	Fasting glucose
HR	Hazard ratio
HbA_{1c}	Glycosylated hemoglobin
IMT	Intima-media thickness
PWV	Pulse wave velocity
SBP	Systolic blood pressure
T2D	Type 2 diabetes
TOD	Target organ damage
UACR	Urin albumin to creatinine ratio

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Author contributions

S.S. and A.D.P designed the study. S.S., M.D.M., N.M., S.C., M.M., G.B., F.D.G.B. researched data and contributed to the discussion. S.S. and A.D.P. performed statistical analysis. S.S. wrote the first draft of the manuscript. S.S., R.S., S.P. contributed to the discussion, reviewed and edited the manuscript. A.V., M.M., F.L.R. contributed to the discussion. A.D.P. supervised the study, contributed to the discussion and reviewed and edited the manuscript. S.P. supervised the study and reviewed the manuscript. All authors approved the final version of the manuscript. A.D.P is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Availability of data and materials

The dataset analyzed during the current study is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Comitato Etico Catania 2, protocol n. 270/C.E. 26th April 2022. Informed consent was obtained from every participant.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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