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Original Article

Ambivalence about the selection of cardiovascular risk stratification tools: Evidence in a type 1 diabetes population

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ABSTRACT

Background: Cardiovascular disease (CVD) is one of the leading causes of death among people with diabetes, however, despite the increasing incidence of CVD, there are few tools for evaluating Cardiovascular Risk (CVR) in the population of patients with Type 1 Diabetes (T1D), with the existing ones diverging in the stratification of risk and in the suggestions for therapeutic conduct.
Methods: A cross-sectional study was carried out with 104 participants diagnosed with T1D, aged 18–40, attending specialized services. The Steno Type 1 Risk Engine and the Cardiovascular Risk Stratification Calculator (CRSC) were used to assess the risk of a cardiovascular event over a 10-year period.
Findings: Of the total sample selected, 62% were female, with a median age of 32 years (IQ 24; 43). There was a large difference between the stratification of CVR between the calculators, and 65.82% of the patients classified as low risk for CVD according to the Steno were identified as intermediate (30, 38.00%) and high risk (35.44%) by the CRSC. The analysis also highlighted a great difference in eligibility for statin use according to the risk stratification of the tools.
Conclusion: The CRSC and Steno tools evaluated and stratified the CVR of the same population with T1D, with there being divergence of the results. It was found that the CRSC tool classified the majority of the sample as high risk. Due to this result, the eligibility to use statins, which is one of the applications of these tools, showed great differences, with the Steno tool presenting less aggressive provisions regarding the prescription of statins in patients with type 1 DM.

1. Introduction

Cardiovascular Disease (CVD) is one of the leading causes of death among people with diabetes [1]. In patients with type 1 diabetes mellitus (T1D), CVD prevalence rates vary considerably based on DM duration, age, sex, and race/ethnicity, however, the available data are less robust when compared to data from patients with type 2 diabetes mellitus (T2D) [2].

Individuals with T1D and with clinical features most often associated with T2D, such as adiposity and insulin resistance, are referred to as having “double diabetes mellitus”, this condition has an additive or synergistic effect on the risk for developing CVD [3–5]. Despite the increasing incidence of CVD, there are few tools for evaluating Cardiovascular Risk (CVR) in the population of patients with T1D (6). In 2016, the validation of the “The Steno Type 1 Risk Engine” tool was made available for patients with T1D, including those under 30 years of age and without previous cardiovascular events or cardiovascular disease [6].

In 2017, the Cardiovascular Risk Stratification Calculator (*Calculadora para Estratificação de Risco Cardiovascular* – CRSC) was made available, which allows the evaluation of CVR in both T1D and T2D individuals, of any age group, including healthy individuals, with or without prior CVD. In addition, this tool also proposes targets for LDL-C and eligibility for statin use [7].

Considering the relevance of the subject, the present study compared the results of CVR evaluation in a population of patients with T1D using the tools “The Steno Type 1 Risk Engine” and the Cardiovascular Risk Stratification Calculator - CRSC and evaluated the eligibility proposals for statin use resulting from the evaluations.

2. Methodology

This was a cross-sectional and descriptive study, where were

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- Age: ≥ 18 years.
- Both sexes
- Diagnosed with DM1 for more than 2 years (in order to exclude patients in the "Honeymoon" period), with follow-up in diabetes center (public or private) for more than two years.
- Patients on basal-bolus insulin therapy, associated or not with oral drugs for the treatment of diabetes.
- Absence of previous cardiovascular disease (CVD)

Fig. 1. Criteria for inclusion and selection of the sample.

evaluated 104 individuals with Type 1 Diabetes (T1D) through the two tools [6,7]. The inclusion criteria defined for the study population were being described in Fig. 1.

For the stratification of cardiovascular risk of the study population, The Steno Type 1 Risk Engine [6] and Cardiac Risk Stratification Calculator (CRSC) instruments [7] were being used, whose risk items are described in Fig. 2.

To evaluate the data used by the calculators the following steps were performed: anthropometric evaluation of the patients following the protocol of Gordon et al. [8], including Body Mass Index (BMI) (weight/height $_2$), stratified as BMI lower than 18.5 - Underweight, between 18.5 and 24.9 - Normal weight, between 25 and 29.9 - Overweight and 30 or above - Obese, waist circumference (WC) (centimeters), waist-to-height-ratio (WC cm/height cm), considering the ratio <0.5, according to the WHO [9,10,11].

Individuals who had practiced some type of physical exercise for ≥3.5 h per week for at least 6 months were considered physically active and those who smoked up to the moment of the interview were considered smokers. The metabolic profile obtained by glycated hemoglobin A1c, total cholesterol and cholesterol fractions, triglycerides, C-reactive protein, and microalbuminuria were defined according to the most recent values at the moment of the interview. The therapeutic regimen of insulin, associated diseases and time since the diagnosis of diabetes were also evaluated.

The study was approved by the Research Ethics Committee of the Faculty of Medical Sciences of the State University of Campinas, authorization no. 1160/2011.

2.1. Statistical analysis

Descriptive statistics were presented by a median (interquartile range) and frequency (percentage). The comparison of variables and calculators for Risk for Cardiovascular Disease was performed using the Mann-Whitney, Kruskal-Wallis, Chi-square test or Fisher's exact test.

For the analysis of the data, the SAS System For Windows (Statistical Analysis System) version 9.4.

2.2. Data availability statement

The data available in Excel and patient medical records used to support the findings of this study are restricted by the Research

Score	Study design	Population	Age	Sex	Variables	Outcome	Risk Categorization
CRSC	A review study performed by 28 experts (cardiologists and endocrinologists), resulting in 59 recommendations	Individuals with significant atherosclerotic disease Individuals with T1D Individuals with T2D	18 to 60 years and over	Female Male	Presence of previous atherosclerotic disease, Sex, Age (>49 years for men and >56 years for women), Duration of diabetes (more than 10 years and diagnosed over 18 years of age). The family history of CAD, Smoking, HP, MS (WHO criteria), GFR <60ml/min/1.73m², Albuminuria >30 mg/g, LDL-c (≥190mg/dl), Subclinical Atherosclerotic Disease	CVD event rate over 10 years (%)	LOW: <10 (Men <38 years and Women <46 years) INTERMEDIATE: 10–20 (Men 38–49 years and Women 46–56 years) HIGH: 20–30 (Men >49 years and Women >56 years or any age if SF or CAT. VERY HIGH: >30 (Any age if CLADc)
Steno	4306 patients monitored at the Steno Diabetes Center in Gentofte, Denmark. With derivation data from the Steno Diabetes Center	Individuals with T1D	18 to 90 years and over	Female Male	Sex, Age (years), Time of diabetes (years), Smoking, Systolic pressure (mmHg), GFR <60ml/min/1.73m², Albuminuria (normo, micro, macro), LDL-c (mg/dL), A1c (%), Regular practice of exercises	CVD event rate over 5 and 10 years (%)	Low: <10% Medium: 10-20% High: ≥20% Categorization of risk based on: Cardiovascular disease: risk assessment and reduction, including lipid modification (2014)

SF - Stratification factors; AS - Subclinical atherosclerosis; CLAD Clinical atherosclerotic disease

Fig. 2. Characteristics of the tools for stratification of cardiovascular risk in patients with diabetes over 10 years.

Ethics Committee of the Faculty of Medical Sciences of the State University of Campinas, authorization no. 1160/2011, in order to protect patient privacy. Data are available from Ticiane Gonçalez Bovi, email - ticianebovi@hotmail.com, for researchers who meet the criteria for access to confidential data.

3. Results

3.1. Characteristics of the patients with type 1 diabetes

A total of 124 patients were selected, of whom 106 met the inclusion criteria. Of the total sample selected, 62% were female, with a median age of 32 years (IQ 24; 43). According to the nutritional assessment, the mean Body Mass Index (BMI) was 25.5 kg/m^2, characterized as Overweight, with a mean of 0.50 for the Waist (cm) height (cm) Ratio, indicating central obesity in the sample studied.

Regarding associated diseases, 20% were diagnosed with SH and 20% with DLP. Concerning complications due to DM, 26% of the patients had Nephropathy diagnoses, of these 18% presented motor sensory peripheral neuropathy and 29% retinopathy. Concerning the behavioral factors, 7% were smokers and 9% ex-smokers and 58% regularly practiced physical activity.

Regarding provenance 77.4% belonged to public service, while 22.6% came from private service. Concerning the therapy used, 42.4% of the patients used multiple insulin applications with a carbohydrate count, 22.6% of which were in the insulin pump and 57.6% used multiple insulin applications. with fixed doses of insulin.

Table 1 presents the detailed (medial and interquartile range) characterization of the evaluated patients.

3.2. Association between the assessments made by the CRSC and Steno calculators for risk of cardiovascular disease

It was observed that the calculators did not use the same criteria for the risk stratification of Cardiovascular Disease, with two major groups (intermediate and high risk) identified by the CRSC and three (low, medium and high risk) by the Steno (Table 2).

In this analysis, 65.82% of the patients classified as low risk for CVD according to the Steno were identified as having intermediate (30.38%) and high (35.44%) risk, by the CRSC. Regarding the intermediate CVR classification, there was only 2.53% agreement between the calculators, with 16.46% ($n = 13$) of those classified as intermediate risk by the Steno being classified as high risk according to the CRSC. Regarding the high risk classification of both calculators, no individual was classified as a High risk for cardiovascular disease according to the Steno as opposed to 15.19% classified by the CRSC.

Table 3 describes the risk stratification of each tool and the percentage of patients in each stratum, showing the difference between the calculators.

Association of behavioral and non-behavioral factors for the risk of cardiovascular disease according to the CRSC and Steno calculators.

Tables 4–7 describe factors associated with cardiovascular disease found through univariate logistic regression analysis.

Factors such as physical activity and smoking were not associated with risk stratification by either of the tools. The presence of Metabolic Syndrome, as well as chronic complications of Diabetes (Nephropathy, Retinopathy, and Neuropathy), were also not associated by the Steno tool.

3.3. Statin eligibility

Using recommendations based on guidelines for statin initiation as primary prevention of cardiovascular diseases [12,13], 100% of the individuals classified by the CRSC would be eligible for statin use, however, 25.9% of patients classified by statin Steno, would be eligible (Table 8).

Table 1
Distribution and characterization of anthropometric data, nutritional and laboratory status of the patients evaluated.

Variable	Patients N	Median (Q1-Q3)
Age (years)	104	32(24–43)
Disease duration (years)	104	19 (8.5–24.0)
Systolic pressure (mmHg)	103	12.0 (11–13)
Capillary glycemia (tests/day) mg/dl	104	4.0 (2.5–6.0)
Body mass index (Kg/m^2)	104	25.3 (22.4–28.5)
Waist circumference (cm)	104	80.2 (76.0–91.2)
Waist/height ratio (0.1) (CC/Alt (cm))	104	0.49 (0.45–0.55)
Neck circumference (cm)	101	35.3 (33.0–37.6)
Glycemia (mg/dl)	101	186 (127–256)
Triglyceride (mg/gl)	104	76 (57–101)
Cholesterol (mg/dl)	104	178 (154–206)
High-density cholesterol (mg/dl)	106	54 (47.0–66.5)
Low-density cholesterol (mg/dl)	104	103 (85.0–126.5)
Microalbuminuria mg/24h	103	7.25 (5.14–18.00)
Glycated hemoglobin (%)	104	8.3 (7.4–9.8)
C-reactive protein (mg/dl)	96	1.8 (0.67–3.90)
Creatinine (mg/dl)	91	0.7 (0.81–0.98)
Glomerular filtration rate (ml/min/1.73m^2)	104	100.2 (82.8–114.9)

* Unbiased estimate of median.

4. Discussion

There are approximately 100 CVD risk assessment calculators for the general population, of which 45 are directed exclusively to the population with Type 2 Diabetes, with few mentioning the T1D variable in their evaluation [6,8,14–16]. The present study is one of the first to propose the analysis of two CVD assessment tools in patients with T1D, as well as, comparing their respective classifications related to statin therapy indications.

It was found that the two instruments considered similar risk factors in their stratifications, however, the results that were obtained with the same population were different. The CRSC tool classified the population as a whole into medium and high-risk strata, while through the Steno it was classified into three categories.

One initial hypothesis is that, despite using similar parameters, the two tools use them in different ways. In the CRSC tool the risk factors are categorized, whereas, in the Steno calculator, the factors are considered for analysis according to the numerical values obtained.

The two calculators evaluated: smoking, systolic pressure, LDL-c, GFR and albuminuria, factors classically related to CVD [17]. In the approach to high blood pressure (HBP) as a risk factor, differences were also found in the two calculators. While the CRSC uses a cutoff point for measured blood pressure values in patients with a diagnosis of hypertension (≥130/85 mmHg) as a risk factor, the Steno tool assesses continuous values and, with this, individuals already medicated could receive a lower risk stratification.

In 2017 a new classification of cutoff points for the diagnosis of HBP was published [21], with Systolic pressure between 130 and 139 mmHg or Diastolic Pressure between 80 and 89 mmHg being considered as Hypertension Stage 1. Thus, individuals who were previously not diagnosed with SH are now diagnosed as having a higher risk factor for CVD, thereby increasing the degree of risk stratification, especially in the population with diabetes mellitus, a disease considered to be a higher factor for CVR. The CRSC calculator considers the diagnosis of hypertension as a risk factor; today

Table 2
Concordance between the CRSC and Steno cardiovascular risk calculators.

CRSC[a]	Steno							
	Low Risk		Average risk		High Risk		Total	
	n	Frequency	n	Frequency	n	Frequency	n	Frequency
Intermediate Risk	24	30.28%	2	2.52%	0	0.00%	26	32.91%
High Risk	28	35.44%	13	16.46%	12	15.19%	53	67.09%
Total	52	65.82%	15	18.99%	12	15.19%	79	100%

[a] Patients with more than 10 years since diagnosis were excluded from the sample, as well as those with the onset of diabetes before the age of 18 years.

Table 3
Number of patients and frequency by two categories of 10-year total cardiovascular disease risk using the CRSC and Steno.

Tool	N	Original Risk Category		
		Low	Medium	High
CRSC	88[a]	0.00%	28.00%	68.18%
Steno	104	74.03%	14.40%	11.50%

[a] Patients with the onset of diabetes before 18 years of age were excluded from the sample.

with the new recommendations it is suggested that blood pressure values above 130 × 90 mmHg would be considered mild hypertension. In this case, patients who were not considered hypertensive, now are, increasing the number of patients in higher scales of cardiovascular risk.

The relevance of LDL-c and its impact both for CVR assessment and eligibility for statin use is indisputable [7,21,22]. In the present study, the diagnosis of Dyslipidemia, rather than the isolated value of LDL-col, was associated with the risk for CVD by both calculators. Findings similar to these were also found in other studies [18,19], thus, it is emphasized that the difference between the tools and their cutoff points could explain the difference in the stratification of CV risk between the tools.

Both tools categorize the assessment of the presence or absence of albuminuria, however, diverge in the use of GFR. While in the Steno the GFR is considered in its absolute values, in the CRSC a GFR less than <60 ml/min/1.73 m^2 would be considered a risk factor. The impact of GFR on CVR is high, according to the literature [20–22] and has aroused researchers' interest in detecting whether earlier forms of renal dysfunction confer a high risk of mortality and cardiovascular disease [23]. Studies on T2D indicate that lower values of GFR coexisting with macroalbuminuria are associated with unfavorable cardiovascular events. At the same time, the association of the reduction of GFR with a high risk for the development of unfavorable cardiovascular outcomes, independent of the ACRR (albumin/creatinine ratio), is well established [24–26] The results of the present study reinforce the importance of use of GFR in the evaluation of CVR, as lower rates of this indicator were associated with higher stratifications for cardiovascular risk.

Although included in classical CVR tools [16,27], the values of glycated hemoglobin (A1c) and its impact on CVR remain controversial [16,28–30]. In the results of the present study, the correlation between their values and an increase in CVR was not verified, in agreement with several studies [31–33]. It was observed that it did not add risk to the patients evaluated by the Steno, which includes this variable.

Regarding age, it should be noted that, unlike the Steno, the CRSC calculator establishes cutoff points that vary according to sex

Table 4
Factors related to health status related to cardiovascular risk according to the CRSC - evaluation between intermediate and high risk.

Variable	*N*	OR	95%CI	*p-value*
Age (years)	*88*	1.202	1.105–1.309	<.0001
Disease duration (years)	*88*	1.326	1.178–1.494	<.0001
Systolic pressure (mmHg)	*87*	1.681	1.188–2.378	.0034
Body mass index (Kg/m^2)	*88*	1.067	0.964–1.180	.2107
Waist/height ratio (0.1) (CC/height (cm))	*88*	4.015	1.625–9.917	.0026
Neck circumference (cm)	*88*	1.119	0.972–1.289	.1173
Menopause	*13*	10.044*	- -	.0139
Arterial hypertension	*88*	27.113*	- -	<.0001
Dyslipidemia	*88*	6.024	1.295–28.035	.0221
Nephropathy	*88*	10.636	2.313–48.897	.0024
Neuropathy	*88*	10.672	1.342–84.844	.0252
Antihypertensive	*77*	6.621	1.404–31.234	.0169
Anticholesterolemic	*77*	11.654	1.452–93.506	.0208
Metabolic syndrome	*84*	9.137*	- -	.0158

CI – confidence interval.

Table 5
Clinical and laboratory data related to cardiovascular risk according to the CRSC - evaluation between intermediate and high risk.

Variable	*N*	OR	95%CI	*p-value*
Glomerular filtration rate (ml/min/1.73m^2)	*80*	0.968 (1.033)	0.947–0.989 1.011–1.056	.0036
Glycated hemoglobin (%)	*87*	0.890	0.715–1.106	.2931
Microalbuminuria mg/24h	*88*	11.854[a]	- -	.0056
		9.825[a]	- -	.0137

[a] Non-biased estimate of the median. CI – confidence interval.

Table 6
Factors related to health status related to cardiovascular risk according to the Steno - evaluation between low, medium and high risk for CVD.

Variable	N	Risk Ratio Steno[a]	OR	95%CI	*p-value*
Age (years)	*104*	Medium Risk High risk	1.2851.463	1.139–1.450 1.237–1.731	<.0001 <.0001
Disease duration (years)	*104*	Medium Risk High risk	1.099 1.177	1.030–1.172 1.086–1.276	.0041 <.0001
Systolic pressure (mmHg)	*103*	Medium Risk High risk	1.671 1.906	1.147–2.433 1.260–2.883	.0075 .0022
Body mass index (Kg/m^2)	*104*	Medium Risk High risk	1.121 0.998	0.990–1.270 0.858–1.160	.0711 .9770
WCH (0.1) (CC/height (cm))	*104*	Medium Risk High risk	2.626 1.900	1.282–5.382 0.857–4.210	.0083 .1140
Menopause[a]	*62*	Medium Risk High risk	67.500 **	6.431–708.519 ** - **	.0004
Hypertension	*104*	Medium Risk High risk	13.519 11.830	3.638–50.238 2.902–48.227	.0001 .0006
Dyslipidemia	*104*	Medium Risk High risk	5.037 5.397	1.450–17.496 1.411–20.647	.0109 .0138
Nephropathy	*104*	Medium Risk High risk	2.067 4.134	0.615–6.949 1.167–14.636	.2407 .0278
Neuropathy	*104*	Medium Risk High risk	0.923 4.287	0.183–4.664 1.153–15.938	.9229 .0298
Retinopathy	*104*	Medium Risk High risk	2.353 3.529	0.734–7.543 1.008–12.358	.1500 .0486
Oral antidiabetics	*104*	Medium Risk High risk	26.908 24.666	2.750–263.329 2.314–262.952	.0047 .0079
Antihypertensive	*102*	Medium Risk High risk	4.52 2.583	1.378–14.829 0.670–9.966	.0128 .1682
Anticholesterolemic	*101*	Medium Risk High risk	5.012 1.909	1.510–16.633 0.445–8.181	.0085 .3838

[a] Relationship: Low Medium and Low-Risk x High Risk.

Table 7
Factors related to cardiovascular risk by the Steno - evaluation between low, medium and high risk for CVD.

Variable	*N*	Risk Ratio Steno[a]	OR	95%CI	*p-value*
Glycated hemoglobin (%)	*104*	Medium Risk High risk	1.105 1.143	0.845–1.444 0.857–1.524	<.0001 <.0001
Glomerular filtration rate (ml/min/1.73m^2)	*104*	Medium Risk High risk	0.967 (1.034) 0.954 (1.048)	0.943–0.992 (1.008)–(1.060) OR inverted 1.086–1.276 (1.018)–(1.080) OR inverted	.0098 .0015

[a] Relationship: Low Medium and Low-Risk x High Risk; CI – confidence interval.

Table 8
Statin therapy eligibility in accordance with different guidelines using different risk scores.

Guidelines and risk Calculator	Statin Eligible Patients (n = 104)
CRSC/European Guidelines and Rewind regarding the use of Statins.	100%
Steno/European Guidelines	25.9%

(men >49 years and women >56 years of age), disregarding a large range of patients whose risk cannot be underestimated due to the longer duration of the disease and exposure to other traditional risk factors for CVD, which could be a bias in the evaluation of patients with T1D when using this stratification criterion [34].

Because of the different classification findings, eligibility for statin use was different between the calculators, although both used the same recommendation [12]. According to the CRSC tool, all the patients were eligible for statin use in contrast to 25.9% according to the Steno, with similar studies also identifying a discrepancy between eligibility for statin use when evaluating the same population with different tools for CVR stratification [19,35].

One possible explanation is based on the CRSC tool itself, in which individuals with diabetes, regardless of the type, are directly classified as intermediate or high CV risk, thus making them always eligible for medication use. This wide eligibility for prescription drugs raises concern, since the early introduction of statins is the subject of several questions, taking into account the presence of adverse effects, including those specific to patients with type 1 diabetes [36].

4.1. Limitations of the study

One of the limitations identified in this study is the comparison between a calculator elaborated for the population with T1D and another that evaluates the CV risk for individuals with and without diabetes (Type 1 or Type 2), the second having a less flexible stratification.

The size of the study series and the non-inclusion of other calculators are believed to be limitations, with further studies on the risk factors and tools for stratification of cardiovascular risk in the population with Type 1 Diabetes being needed.

5. Conclusion

The CRSC and Steno tools evaluated and stratified CVR in the same population with Type 1 Diabetes, with there being a divergence in the results. The difference found was that the CRSC tool classified the majority of the sample as high risk. Due to this result, the eligibility to use statins, which is one of the applications of these tools, showed great differences, with the Steno tool presenting less aggressive proposals regarding the prescription of statin therapy in patients with type 1 DM. Prospective CVR studies with type 1 DM patients will account for whether or not more aggressive statin prescription measures are warranted. At present, according to current guidelines, patients at low risk are not eligible for statin use, with the results indicating that these patients are not identified by the CRSC tool.

Conflicts of interest

The authors declares that there is no conflict of interest regarding the publication of this paper.

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