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IMPORTANCE OF DIABETES MELLITUS IN THE RISK STRATIFICATION OF CORONARY ARTERIAL DISEASE AND GLOBAL CARDIOVASCULAR RISK

IMPORTÂNCIA DO DIABETES MELLITUS NA ESTRATIFICAÇÃO DO RISCO DE DOENÇA ARTERIAL CORONÁRIA E RISCO CARDIOVASCULAR GLOBAL

Maria Cristina de Oliveira Izar[1]
Ana Paula Marte Chacra[2]
Hermes Toros Xavier[2]

1. Escola Paulista de Medicina da Universidade Federal de São Paulo (UNIFESP), São Paulo, SP, Brazil.
2. Instituto do Coração, Faculdade de Medicina da USP (InCor), São Paulo, SP, Brazil.

Correspondence:
Maria Cristina de Oliveira Izar
Rua Loefgren, 1350, Vila Clementino, São Paulo, SP, Brazil. 04040-001.
mcoizar@terra.com.br
mcoizar@cardiol.br

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ABSTRACT

Diabetes mellitus can be considered an epidemic disease. Adults with diabetes have two to three times higher rates of cardiovascular disease than those observed in non-diabetic adults. The recognition that diabetes is a heterogeneous disease in relation to cardiovascular risk was fundamental for the correct identification of individuals at higher risk, who require more intensive pharmacological intervention, and those at lower risk, where the use of non-pharmacological strategies alone in an initial phase is optional. More precise risk stratification tools, the appropriate use of screening methods for tracking ischemia in the asymptomatic patient, and the indication of imaging tests will be summarized in this review. Treatment based on global risk factor control includes the modern approach for the patient with diabetes, aiming at reducing both macro- and microvascular events.

Keywords: Diabetes mellitus; Coronary artery disease; Myocardial infarction; Stroke.

RESUMO

O diabetes mellitus é uma doença epidêmica. Os adultos portadores de diabetes têm taxas de doenças cardiovasculares duas a três vezes maiores do que aquelas observadas em adultos não diabéticos. O reconhecimento de que o diabetes é uma doença heterogênea em relação ao risco cardiovascular foi fundamental para a identificação correta dos indivíduos sob maior risco, os quais necessitam de tratamento farmacológico mais intensivo, e daqueles cujo risco é menor, em que o uso de medidas não farmacológicas isoladamente em uma fase inicial é opcional. Ferramentas para estratificação de risco mais precisas, uso apropriado de métodos de rastreamento de isquemia no paciente assintomático e indicação dos métodos de imagem são brevemente revisados neste capítulo. O tratamento de todos os fatores de risco inclui a moderna abordagem do paciente com diabetes, visando a redução de eventos macro e microvasculares.

Descritores: *Diabetes mellitus; Doença da artéria coronariana; Infarto do miocárdio; Acidente vascular cerebral.*

INTRODUCTION

Diabetes mellitus (DM) is an epidemic disease and, historically, adult patients with diabetes have cardiovascular disease (CVD) occurrence rates that are two to three times higher than those observed in adults without diabetes.[1]

The risk of cardiovascular events increases continuously with increasing fasting blood glucose levels, even before the diagnosis of diabetes.[2,3] A few countries in North America, Scandinavia, and the United Kingdom have studied the trends in the incidence of cardiovascular events, such as myocardial infarction, ischemic stroke, or cardiovascular mortality, and have reported large reductions in their occurrence rates over the past 20 years among people with type 1 and type 2 diabetes[4]. However, the reduction rates are lower than those observed among patients without diabetes. These reductions have been attributed to the reduction in the prevalence of the smoking habit, as well as the better management of diabetes and the associated cardiovascular risk factors.

Recognizing that diabetes is a heterogeneous disease with respect to CVD risk is fundamental. Not all diabetes patients belong to high or very high-risk categories, with a considerable percentage comprising young patients with no classic risk factors and who can be classified adequately as having low or intermediate CVD risk. Thus, it is important to identify those at a greater risk, who require more intensive pharmacological treatment, and those

whose risk levels are lower, in whom it is possible to use non-pharmacological measures alone at an early stage.

Significant studies on CVD prevention and treatment in patients with diabetes have contributed to the evolution of the approach towards the care of patients with diabetes in terms of primary and secondary prevention.[5] More precise risk stratification tools, new classes of lipid-lowering drugs and antihyperglycemic drugs that provide safety and even cardiovascular protection, some of which demonstrate a reduction in mortality, are part of the new approach to diabetes patients.

The Brazilian Society of Diabetes (SBD), the Brazilian Society of Cardiology (SBC) and the Brazilian Society of Endocrinology and Metabolism (SBEM) formed a panel of specialists comprising cardiologists and endocrinologists to review the best available evidence and formulate a guideline containing practical recommendations for the risk stratification and prevention of CVD in DM cases. The main innovations included considerations on the impact of lipid-lowering and antihyperglycemic therapy on CVD risk, a practical approach based on risk factors to guide the use of statins, including new definitions of low-density lipoprotein cholesterol (LDL-c) and non-high-density lipoprotein cholesterol (HDL-c) targets, and an evidence-based approach to assess silent myocardial ischemia and subclinical atherosclerosis in diabetes patients. The positioning of these societies on diabetes and CVD prevention reviewed the best evidence currently available and proposed a risk-based practical approach to the risk stratification and treatment for diabetes patients.[6]

CARDIOVASCULAR RISK STRATIFICATION

Patients with type 1 and 2 diabetes are divided into four major categories by CVD risk: low, intermediate, high and very high (Table 1) based on age, and the presence of risk stratifiers (ER) (Table 2), subclinical atherosclerotic disease (DASC), (Table 3) or clinical atherosclerotic disease (CLAD) (Table 4). The 10-year cardiovascular event rates in the low, intermediate, high and very high risk groups are estimated at <10%, 10-20%, 20-30% and >30%, respectively. (Table 1)[6]

Low and Intermediate Risk

The low and intermediate risk categories are based only on age and SF (Table 2). SCAT (Table 3) and CLAD (Table 4) are not present in these risk groups. In a retrospective cohort

Table 2. stratification factors (SF) in patients with diabetes mellitus.

Age >49 years for men or >56 years for women[7]
[a]Duration of diabetes greater than 10 years[8]
[b]Family history of premature coronary artery disease[9]
[c]Presence of metabolic syndrome defined by the IDF[10]
Treated or untreated hypertension[11]
[d]Current smoking[12]
Estimated glomerular filtration rate lower than 60 mL/min/1.73 m^2 [13]
Albuminuria above 30 mg/g creatinine[14]
Autonomic neuropathy[15]
Diabetic retinopathy[16,17]

HDL-c, high-density lipoprotein cholesterol; IDF, International Diabetes Federation; [a]Valid for patients with the diabetes onset age greater than 18 years;[b] Family history of premature coronary disease is defined by the presence of coronary events in first-degree relatives (father, mother or siblings) before age 55 years for men or age 65 years for women; [c] The definition of the International Diabetes Federation IDF of metabolic syndrome consists of: abdominal circumference ≥94 cm for men and ≥ 80 cm for women, and two or more of the following criteria; (1) triglyceride level ≥150 mg/dL for men and women; (2) HDL-c <40 mg/dL in men and <50 mg/dL in women; (3) blood pressure ≥130/85 mmHg or treatment for hypertension; and (4) fasting blood glucose ≥110 mg/ dL; [d] Current smoking is defined as the last episode occurring less than 1 year before the time of stratification. Adapted from Faludi et al.[6]

Table 3. Subclinical atherosclerotic disease.

[a]Coronary artery calcium score (CAC) >10 U Agatston
Carotid plaque (intima-media thickness > 1.5 mm)[18]
[b]Coronary computed tomography angiography (CCTA) with the presence of plaque[19]
Ankle-brachial index <0.9[20]
[c]Abdominal aortic aneurysm (AAA)[21-25]

[a] When available, CAC measurement should be the preferred modality; [b] CCTA should not be performed routinely in asymptomatic patients; [c] Patients with AAA are at high risk for cardiovascular morbidity and mortality due to the presence of habitual risk factors and comorbidities associated with the aneurysm. Adapted from Faludi et al.[6]

Tabela 4. Clinical atherosclerotic disease (CLAD).

Acute coronary syndrome
Acute myocardial infarction or unstable angina
Stable angina or a history of acute myocardial infarction
Atherothrombotic stroke or transient ischemic attack
Coronary, carotid or peripheral revascularization.
Peripheral vascular insufficiency or limb amputation
Severe atherosclerotic disease (stenosis >50%) in any vascular territory

Adapted from Faludi et al.[6]

Table 1. Categories of cardiovascular risk in patients with diabetes.

Risk category	10-year CAD event rate (%)	Age	Condition
Low	<10	Man <38 years	No risk stratifiers (SF)[a]
		Woman <46 years[7]	No subclinical atherosclerotic disease (SCAT)[b]
Intermediate	10-20	Man 38-49 years	No clinical atherosclerotic disease (CLAD)[c]
		Woman 46-56 years	
High	20-30	Man > 49 years or any age in the case of ER or DASC	Risk stratifiers (SF)[a]
		Woman > 56 years or any age in the case of ER or DASC	Subclinical atherosclerotic disease (SCAT)[b] No clinical atherosclerotic disease (CLAD)[c]
Very high	>30	Any age in the case of DACL	Clinical atherosclerotic disease (CLAD)[c]

CAD: Coronary artery disease; [a] Risk stratifiers (Table 2); [b] Subclinical atherosclerotic disease (Table 3); [c] Clinical atherosclerotic disease (Table 4). Adapted from Faludi et al.[6]

study in the Ontario population, 379,003 people with diabetes were included and followed-up for an average of eight years, until the first event of myocardial infarction or all-cause death.[7] It was observed that the transition from low to intermediate risk occurred at age 38 years for men and 46 years for women. The transition from intermediate risk to high risk occurred at ages 49 and 56 years, respectively, in men and women.[7] Therefore, diabetes patients without clinical or subclinical CVD and without ER are considered as having an intermediate risk at ages 38-49 years (in men) or 46-56 years (in women), and low risk if they are younger, in the absence of SF, SCAT or CLAD.[7]

High Risk

The high-risk group of diabetes patients is defined by the presence, at any age, of at least one SF (Table 2) or SCAT indicator (Table 3) in the absence of CLAD (Table 4). In the absence of these conditions, a patient with diabetes is also considered as having a high risk when his/her age is greater than 49 years in men or 56 years in women.[7]

Very High Risk

The very high risk group includes patients who, at any age, have CLAD as defined in Table 4.

Choosing risk stratifiers in patients with diabetes mellitus

The choice of risk stratifiers was defined based on studies that demonstrated their impact on the occurrence of CVD in patients with diabetes. Age > 49 years in men and > 56 years in women was defined based on a population-based retrospective cohort study, conducted in Ontario, Canada, on 379,000 participants with diabetes and 9,018,082 people without the disease, followed from 1994 to 2000 for the evaluation of cardiovascular events. The transition to the high-risk category occurred earlier in men and women with diabetes than in those without the disease (mean difference of 14.6 years).[7]

In terms of outcomes such as acute myocardial infarction, stroke, or death from any cause, men and women with diabetes entered the high-risk category at 47.9 and 54.3 years, respectively. When the definition of CVD was more comprehensive, including coronary or carotid revascularization, the ages at transition to the high-risk category were 41.3 and 47.7 years for men and women, respectively.[7] That study concluded that diabetes provides a risk equivalent to an additional 15 years of age. However, in general, younger people with diabetes (aged 40 years or younger) do not appear to be at a high risk for cardiovascular events. Age should be considered a target for cardiovascular risk reduction.

The impact of age on the onset of diabetes and its duration were evaluated in a prospective study. A total of 4,045 male participants aged 60-79 years were included. Both early-onset and late-onset diabetes were associated with a significantly increased risk of cardiovascular events and all-cause mortality compared to non-diabetic men without prior CVD, even after adjustment for both conventional risk factors and new risk markers (C-reactive protein, von Willebrand factor and renal dysfunction). Only men with early-onset diabetes (associated with a disease duration greater than 16.7 years) presented a risk similar to that in those with previous infarction and without diabetes. The authors concluded that both early-onset and late-onset diabetes are associated with an increased risk of major cardiovascular events and mortality, but only those with early-onset diabetes (with a disease duration greater than 10 years) seem to behave as equivalent of cardiovascular risk.[8]

Family history of coronary artery disease (CAD)[9] was evaluated in a prospective cohort of postmenopausal women with diabetes but with no vascular disease at the baseline. Family history was defined as the presence of infarction in a first-degree relative. Incident coronary disease was defined as non-fatal infarction, coronary revascularization or coronary death. Over a follow-up of 7.3 (±1.8) years, 14.3% of the participants presented a coronary event. The risk of a coronary events was 50% higher (hazard ratio [HR] = 1.50, 95% confidence interval [CI]: 1.20 – 1.87, p = 0.0003) in those with a positive family history of myocardial infarction in at least one first-degree relative and 79% higher (HR = 1.79, 95% CI: 1.36 – 2.35, p < 0.0001) if two first-degree relatives had a myocardial infarction, compared to participants with no family history of myocardial infarction, after adjustment for other covariables. The risk of coronary heart disease increased with systolic blood pressure (HR = 1.01, 95% CI: 1.003–1.02, p = 0.001), but decreased with elevated diastolic pressure (HR = 0.98, 95% CI: 0.97–0.999, p = 0.005) and participation in physical activity two or more times a week (HR = 0.70, 95% CI: 0.52–0.93, p = 0.02). The results suggested that having a family history of myocardial infarction was a predictor of coronary disease in postmenopausal women with diabetes.

A meta-analysis of 87 prospective studies including 951,083 participants, in which the presence of metabolic syndrome according to the definitions of the NCEP III or rNCEP and the risk of CVD were evaluated, concluded that the presence of metabolic syndrome was associated with a two-fold increase in the risk of cardiovascular events and 1.5-fold in all-cause mortality.[10]

Hypertension is the condition most commonly found in primary prevention and is associated with myocardial infarction, stroke, renal failure, and death if not detected early and treated appropriately. Its occurrence in people with diabetes is associated with an increased risk of cardiovascular events. Recent international guidelines modified the values indicative of normal blood pressure (<120 / < 80 mmHg), high blood pressure (120-129 / < 80 mmHg), stage 1 hypertension (130-139 or 80-89 mmHg) and stage 2 hypertension (≥ 140 / ≥ 90 mmHg).[11] Pharmacological therapy in these patients should be initiated if the blood pressure is > 130/80 mmHg and the target to be achieved is < 130/80 mmHg. These recommendations apply to most cases, including patients with and without diabetes.[11]

Few epidemiological studies have investigated the importance of cardiovascular risk factors in the risk of coronary events in both sexes. In particular, it is not clear whether the smoking habit is associated with an increased risk of coronary artery disease in men and women. The associations between smoking, serum lipids, blood pressure and myocardial infarction were examined in a population-based prospective study with 11,843 men and women aged between 35 and 52 years at the baseline. Over a 12-year follow-up period,

there were 495 cases of myocardial infarction in men and 103 in women. The incidence of myocardial infarction was 4.6 times higher in men, but this increased by 6 times in women and 3 times in men who smoked at least 20 cigarettes a day, compared to non-smokers. The event rate in women considered heavy smokers exceeded the event rate in men who never smoked. In the multivariate analysis, smoking was identified as an even greater risk factor in women (relative risk, 3.3, 95% CI, 2.1 – 5.1) than men (relative risk, 1.9, 95% CI, 1.6 – 2.3). Among those younger than 45 years at the baseline, the differences between the sexes, in terms of smoking, were higher (women: relative risk, 7.1, 95% CI, 2.6 – 19.1, men: relative risk, 2.3, 95% CI, 1.6 – 3.2). Total cholesterol, HDL-c, and systolic blood pressure were also highly predictive of such events in both sexes.[12]

There is considerable controversy over the use of estimated glomerular filtration rate (eGFR) and albuminuria to define chronic kidney disease (CKD) and classify it in stages. A meta-analysis was performed to investigate the combined and independent associations of eGFR and albuminuria with mortality.[13] Data on all-cause mortality and cardiovascular mortality in studies with more than 1,000 participants and containing baseline information on eGFR and urinary albumin concentrations were selected. Regression models were used to estimate the risk ratio for the global and cardiovascular mortality associated with eGFR and albuminuria, adjusted for possible confounding factors. It was observed that an eGFR < 60 mL/min/1.73 m^2 and albumin/creatinine ratio of 1.1 mg/mmol (10 mg/g) or higher were independent predictors of mortality risk in the general population. The study evaluated quantitative data from both renal function measurements to assess the risk and definition of the CKD stages.[13] In an analysis of the HOPE study,[14] the degree of albuminuria was a risk factor for cardiovascular events in individuals with or without diabetes; the risk increased with an increasing albumin/creatinine ratio, starting at levels well below the threshold for microalbuminuria. Thus, albuminuria research has identified the individuals at risk for cardiovascular events.

In the Action to Control Cardiovascular Risk in Diabetes study, the presence of cardiac autonomic neuropathy (CAN) was evaluated as a predictor of mortality. During a 3.5-year follow-up period, there were 329 all-cause deaths. In the adjusted analysis, participants who presented CAN were 1.55-2.14 times likelier to die than participants without CAN, depending on the definition used for CAN ($p < 0.02$ for all). The effect of allocation for intensive treatment on total and cardiovascular mortality was similar among participants with or without the presence of CAN at the baseline.[15] In the same study,[16] both the severity of retinopathy and its progression were determinants of the incidence of cardiovascular events. The retina may provide an anatomical index of the effects of metabolic and hemodynamic factors on future cardiovascular outcomes. A meta-analysis of observational studies[17] demonstrated that the presence of diabetic retinopathy was associated with an increased risk of all-cause mortality and cardiovascular events in both type 1 and type 2 diabetes.

The usefulness of carotid plaque markers, such as the sum of plaque thickness (P_S) or the maximum plaque thickness (P_{-max}), in combination with the intima media thickness of the common carotid artery (cIMT), was investigated in type 2 diabetes patients without prior CVD to predict the risk of CAD.[18] Although P-max and PS in the carotid arteries have proved to be useful markers for the detection of coronary disease, combining these measures with cIMT provides a screening method that is significantly superior for the detection of CAD in individuals with asymptomatic diabetes.

In individuals with asymptomatic diabetes, the assessment of CAD by coronary computed tomography allows for the prediction of incremental risk, better discrimination, risk reclassification according to the type and extension of affected vessels.[19]

Regarding the ankle-brachial index (ABI), low ABI values were independently associated with a high risk of all-cause mortality and cardiovascular mortality in Chinese patients with type 2 diabetes. ABI can be considered an ideal tool for the prediction of mortality in patients with diabetes.[20] Likewise, the presence of abdominal aortic aneurysm in patients with diabetes increases the risk of cardiovascular events.[21-25]

THERAPEUTIC GOALS FOR DYSLIPIDEMIA IN DIABETES PATIENTS

After the stratification of the cardiovascular risks in patients with diabetes, it is necessary to define the therapeutic goals, and consider the use of statins as the first choice in the approach for dyslipidemia in such patients.

Therapeutic targets for low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol

The therapeutic targets for LDL-c (primary target) and non-HDL-c (secondary target) are presented in Table 5.

Use of appropriate doses of statins to achieve the recommended goals

Data on the use of statins in appropriate doses to achieve the recommended goals are presented in Table 6.

Statin recommendation according to cardiovascular risk in patients with diabetes

Data on the recommendation of statins according to cardiovascular risk in patients with diabetes are presented in Table 7.

SPECIAL SITUATIONS

Familial hypercholesterolemia

It is recommended that patients with diabetes and LDL-c levels > 190 mg/dL be investigated for familial hypercholesterolemia (FH). [I, C].[6]

The diagnosis of FH in patients with diabetes should always be considered and investigated when the concentrations of LDL-c are above 190 mg/dL. LDL-c concentrations > 250 mg/dL in patients aged 30 years and older, LDL-c > 220 mg/dL in patients aged 20-29 years, and LDL-c > 190 mg/dL in patients younger than 20 years indicate approximately an 80% probability of FH in the screening of the general population.[26,27]

Table 5. LDL-cholesterol and non-HDL-cholesterol targets in patients with diabetes according to cardiovascular risk.

Risk Level	No statin	Treatment with statin	
	% reduction	LDL-c (mg/dL)	non-HDL-c (mg/dL)
Low	30-50	<100	<130
Intermediate	30-50	<100	<130
High	>50	<70	<100
Very high	>50	<50	<80

HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; Adapted from Faludi et al.[6]

Table 6. Mean of the expected percentage of LDL-c reduction with statin use.

Statin (in mg)	Expected mean of LDL-c reduction (%)	Expected mean of LDL-c reduction (%)	Expected mean of LDL-c reduction (%)
	<30	30–50	≥50
Simvastatin	10	20–40	40 + ezetimibe
Pravastatin	10–20	40–80	–
Fluvastatin	20–40	80	–
Atorvastatin	–	10–20	40–80
Rosuvastatin	–	5–10	20–40
Pitavastatin	1	2–4	–
Lovastatin	20	40	–

LDL-c, low-density lipoprotein cholesterol; adapted from Faludi et al.[6]

Table 7. Recommendation for treatment with statin according to the category of cardiovascular risk in diabetes patients.

Risk category	Treatment with statin
Low	Optional[a]
Intermediate	Recommended
High	Highly recommended
Very high	Mandatory

[a]Optional means that non-pharmacological (lifestyle) measures are acceptable as long as an LDL-c target <100 mg/dL is achieved and maintained. For patients with LDL-c levels > 160 mg/dL, statins are advisable in any risk category. Adapted from Faludi et al.[6]

Dialytic chronic kidney disease

Due to the lack of evidence on the benefits of lipid-lowering therapy with statins in patients with chronic renal failure on dialysis, the start of statin use is not recommended in patients with diabetes and chronic renal failure on dialysis, without CLAD (Table 4). Statin use may be associated with a higher risk of stroke [III, A]. However, in patients with chronic renal failure already on statin therapy prior to dialysis, statin use should not be withdrawn.[28,29]

Heart failure

In patients with diabetes and heart failure class III-IV, the initiation of statin therapy is not recommended because there is no clear evidence on the associated benefits in this group of patients [III, A].[6]

Hypertriglyceridemia

In patients with diabetes and mild-to-moderate hypertriglyceridemia (TG 150-400 mg/dL), the combined use of statin and fibrate is usually not recommended for cardiovascular risk reduction. However, in specific situations of patients with triglyceride levels > 204 mg/dL and HDL-c levels <34 mg/dL, a combination of fenofibrate and statin may be considered when lifestyle modifications have failed [IIa, B].[30]

SUBCLINICAL ATHEROSCLEROSIS IN DIABETES PATIENTS

Patients with DM present heterogeneous cardiovascular risk, resulting from their clinical characteristics, metabolic alterations and interaction between traditional risk factors, genetic predisposition and environmental factors. The presence of an individual risk gradient leads to complexity and difficulty in the risk stratification of this population; however, the knowledge of individual cardiovascular risk is crucial for the establishment of appropriate strategies for the management of the disease and its complications.

Considerations on the use of risk scores in patients with diabetes

The method used for the evaluation of the risk of coronary heart disease in asymptomatic diabetes patients for primary prevention is based on clinical scores such as the Framingham risk score (FRS) and United Kingdom Prospective Diabetes Study (UKPDS) score, among others, based on traditional risk factors.[31] The FRS uses age, sex, blood pressure, total cholesterol and HDL-c values, and the presence of DM to calculate the risk of infarction or death from CAD in 10 years.[32] Although useful, its predictive value is modest when evaluated by the C statistic (0.70-0.75). A risk score should discriminate patients who may or may not have an outcome in the future. The discriminatory analysis is measured by the area under the receiver operating characteristic (ROC) curve, also called the area under the curve (AUC), when it comes to prognosis.[33] Due to the low performance of the various risk markers in increasing the AUC, that is, of providing a greater discriminatory power among those who will or will not have an event, other approaches, such as reclassification, have analyzed the predictive ability of such markers. Reclassification evaluates the ability of a new test, when added to a model, to redistribute a participant to a higher or lower risk category.[34]

Risk prediction scores establish the risk category of a patient, in addition to reporting on prognoses, as well as the risks and benefits of individual preventive treatments. Therefore, accurate risk estimation is important.

The multivariate equations available for the measurement of cardiovascular risk in diabetes patients were derived from the general population or from populations with diabetes and have been used in several cohorts. In the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation study, patients were stratified using the Framingham and UKPDS risk equations. When compared, these equations overestimated the risk in the population of diabetes patients, in addition to presenting a limited power of discrimination between high and low-risk individuals. This is one of the examples that confirms the difficulty of performing risk stratification using

clinical scores, since most coronary events continue occurring in low or intermediate risk patients.[35] The limitation of clinical risk scores stem from the pathophysiology of atherosclerosis itself. Mendelian randomization studies and longitudinal cohort studies with young populations, in addition to autopsy studies, have shown that exposure to the risk of atherosclerosis occurs early, varies in intensity throughout life, and includes genetic and environmental factors that are unaccounted for. A single measurement of traditional risk factors in an adult fails to quantify time-dependent risk exposure. The risk of CVD would be more accurately expressed as a function of the cumulative exposure to all these risk factors throughout life.[36]

New biomarkers

The use of new biomarkers may identify other pathophysiological pathways, such as high sensitivity C-reactive protein (hsCRP) levels and the presence of inflammation in the etiopathogenesis of atherosclerosis. However, these biomarkers are not very specific because they change in several inflammatory conditions, and display variability of measurement and modest capacity in the reflection of the accumulated exposure to risk. They add little to the FRS regarding risk stratification.[36] The Emerging Risk Factors Collaboration evaluated 250,000 individuals, in which the measurement of us-CRP (high-sensitivity C-reactive protein) was added to the FRS. The risk reclassification was only moderately improved at 1.5%, and it was necessary to measure hs-CRP in 500 people at intermediate risk to predict the occurrence of a cardiovascular event in 10 years; this is not very cost-effective.[37]

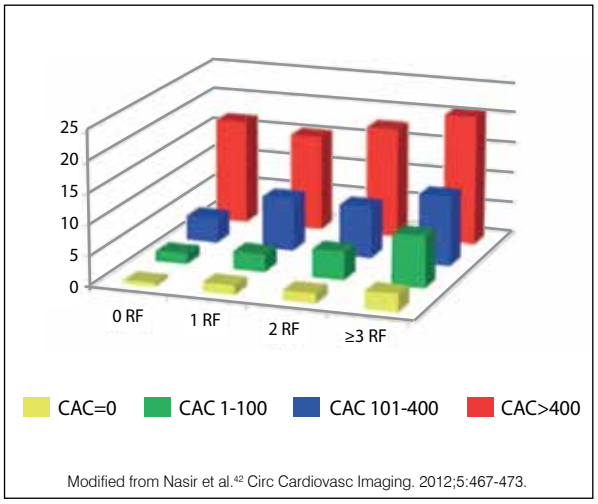
Subclinical atherosclerosis

Another alternative to improve risk prediction involves the use of imaging, which directly measures the burden of atherosclerosis. Coronary artery calcification (CAC) is part of the development of atherosclerosis, occurring almost exclusively in atherosclerotic arteries; it is absent in normal vessel walls.[38] The degree of CAC is determined by electron beam and multi-detector computed tomography.[39] The images of the atherosclerotic plaque burden customize risk assessment by integrating the cumulative effect between genetic or epigenetic risk determinants with measurable (blood pressure and serum cholesterol) and non-measurable risk factors (air pollution and secondhand smoke), by directly visualizing the vascular bed. The use of imaging methods in the assessment of atherosclerosis may reduce the proportion of inaccuracies in the quantification of risk exposure, which sometimes begins at a very early stage. Direct visualization of the vascular bed allows clinicians to identify individuals who, for unclear reasons, do not develop atherosclerosis despite having an apparently significant risk, as well as individuals who, in the absence of risk factors, develop atherosclerotic disease. The coronary artery calcium score has a strong correlation with the total atherosclerotic coronary burden, and is an independent predictor of CVD risk.[40,41]

Risk heterogeneity: traditional risk factors versus subclinical atherosclerosis

Even in the presence of a direct relationship between the risk predicted by the FRS, according to the number of risk factors, and CAC severity, its distribution within the groups stratified by risk factors is heterogeneous.[42] Atherosclerotic plaque burden is not a mandatory finding in older patients or those with many risk factors.[43-46] Similarly, young patients with no or one risk factor may have an increased atherosclerosis plaque burden. This phenomenon was demonstrated in an observational study with approximately 44,000 asymptomatic individuals without previous coronary disease, who performed CAC and were followed-up for an average period of 5 years. Among individuals with no risk factors, 53% had a coronary artery calcium score ≠ '0' and, when adjusted for age and sex, the increased calcification was associated with a total mortality risk that was three to 18 times higher than those with CAC=0. The presence of a coronary artery calcium score higher than 400 was associated with a significant increase in mortality in the group with no risk factors, especially when compared to the group with three or more risk factors and with a coronary artery calcium score = 0. This study demonstrated that coronary artery calcium scores of 100 or higher were markers of mortality in all groups stratified by the number of risk factors (Figure 1). Such findings challenge the exclusive use of traditional risk assessment algorithms, as the intensity of preventive therapeutic measures is determined by patient risk.[45,46]

Although DM is recognized as an important risk factor for CAD, it remains controversial to consider individuals with diabetes and no coronary disease at a similar risk than those with prior myocardial infarction without diabetes. Previous studies have shown that the risks of CAD among CAD-free diabetes patients and non-diabetic individuals with prior myocardial infarction are equal.[47,48] However, in a meta-analysis of 13 studies, including 45,108 patients, the presence of diabetes was not indicative of coronary heart disease risk. Diabetes patients with no history of myocardial infarction had a 43% lower risk of coronary heart disease than non-diabetic patients with prior myocardial infarction.[49] Recently, a prospective study that followed 1,586,061 adults over 10 years observed that the risk of new coronary events was lower in patients with diabetes and no previous CAD than those with CAD and without diabetes.[50]



Modified from Nasir et al.[42] Circ Cardiovasc Imaging. 2012;5:467-473.

Figure 1. Association of coronary artery calcification and traditional risk factors in the prediction of the risk of all-cause mortality in asymptomatic individuals.

The heterogeneity in the risk of patients with diabetes is related to differences in the typical clinical characteristics of the disease, which include age of onset, as well as duration and severity of diabetes, as measured by fasting blood glucose levels, in addition to concomitant cardiometabolic risk. In recent years, despite evolutions in therapy, the cardiovascular mortality associated with type 2 diabetes is extremely high. Subgroups of patients with a relatively low risk may be overly treated, while others with a high risk may require more intense risk-factor modifications. These differences reflect the variability of the subclinical atherosclerosis plaque burden in this population.[6]

Methods for the evaluation of subclinical atherosclerosis in diabetes mellitus

Endothelial function, microvascular reactivity, and the measurement of cIMT and CAC degree may already be altered even in patients with a recent diagnosis of DM. As they are present from the early stages of atherosclerotic lesion development, they can be considered early markers of subclinical atherosclerosis. The stratification of cardiovascular risk with these markers aims to improve risk prediction. Some techniques used for the early detection of subclinical atherosclerosis are the coronary artery calcium score and cIMT.[6]

Prevalence of coronary artery calcification and its association with diabetes risk factors

The prevalence of CAC in asymptomatic diabetes patients without prior CAD is higher than in non-diabetic patients. In addition, risk predictors associated with CAC is also higher in diabetes compared with non-diabetic subjects.[51] In non-diabetic populations, an association was observed between traditional risk factors and CAC among younger and older groups; the strength of this association increased in proportion to the number of risk factors present.[51] The presence of CAC was also associated with serum apolipoprotein B concentrations in asymptomatic men.[52] In addition, CAC correlated with intra-abdominal adiposity and measurements of insulin resistance.[53] No association was demonstrated between CAC and hs-CRP.[54]

In three cohorts of male and female individuals with type 2 diabetes of distinct ethnicities, one from the United States of America[55] and two from the United Kingdom,[56,57] cardiovascular risk factors including age, male sex and systolic BP were correlated with CAC, except smoking. Triglyceride-rich lipoproteins correlated independently and significantly with CAC.[55] In two of these cohorts, the presence of CAC was associated with statin therapy.[56,57] CAC was also associated with the waist-to-hip ratio,[56] but not with glycated hemoglobin (HbA1c) levels and microalbuminuria.[56,57]

Regarding the new biomarkers, the inflammatory marker interleukin (IL)-6, but not hs-CRP,[58] and the presence and extent of diabetic retinopathy were related to CAC.[59]

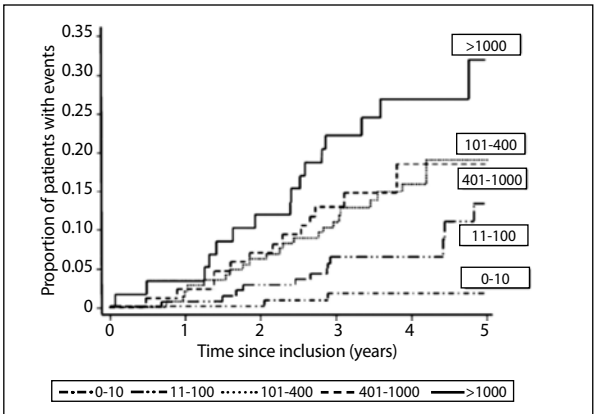
Coronary calcium score and prediction of cardiovascular events in type 2 diabetes mellitus

Given the prevalence of CAC and its association with risk factors, some studies have evaluated the addition of the coronary artery calcium score to predictive risk models. In the Multi-Ethnic Atherosclerosis Study (MESA) study, the risk factors and calcium score were evaluated in 8,722 white, black, Hispanic, and Chinese people, followed-up for 3.8 years. The areas under the ROC curve were larger when the calcium score was added to the classic risk factors. The presence of CAC was strongly predictive of CAD, regardless of the classic risk factors for all the ethnic groups included in the study. In the subgroups of diabetes patients, the higher the CAC, the greater the risk of cardiovascular events.[42]

The Patients With Renal Impairment And Diabetes Undergoing Computed Tomography study prospectively evaluated the predictive value of the coronary artery calcium score for cardiovascular events in patients with type 2 diabetes.[60] The study followed 589 patients with diabetes, without prior CVD, and with a mean age of 63.1 years, for 4 years (Figure 2). The higher the coronary artery calcium score, the greater the risk of cardiovascular events. A total of 23% of the individuals had a coronary artery calcium score <10 and low cardiovascular risk. Only 9% had a coronary artery calcium score above 1000, accounting for 25% of all the coronary events. The only predictive risk factors for primary outcomes, regardless of CAC, were systolic hypertension and the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index. There was a significant increase in the area under the ROC curve from 0.63, when the UKPDS risk score was used, to 0.73 ($p = 0.03$) after the addition of the coronary artery calcium score. This study also concluded that a coronary artery calcium score <10 is useful for the detection of low-risk individuals in this population.

Raggi et al.[61] evaluated 10,377 asymptomatic individuals (903 with diabetes) in whom the coronary artery calcium score was calculated and who were followed-up for 5 years. In diabetes patients, the mean coronary artery calcium score was higher than in the non-diabetic people (281 ± 567 versus 119 ± 341, $p<0.0001$). The higher the calcium score, the higher the mortality in diabetes patients. However, at a coronary artery calcium score = 0, the survival rate was similar in patients with and without diabetes (98.8% vs 99.4%, respectively, $p = 0.5$).

These associations were confirmed by a meta-analysis of eight cohort studies[17] that investigated the association



Modified from Elkeles et al.[60] Diab Med 2004;21:1129-34.

Figure 2. Proportion of patients with events according to the calcium score categories, during follow-up.

of CAC with mortality and cardiovascular events. The study included 6,521 type 2 DM patients with an average follow-up of 5.18 years. The numbers of events in patients with a coronary artery calcium score higher and lower than 10 were compared. The prevalence of a coronary artery calcium score lower than 10 was 28.5%. The relative risk of all-cause mortality or CVD events was 5.47 (95% CI 2.59-11.53 p <0.001). People with a coronary artery calcium score <10 presented a 6.8-fold lower risk of cardiovascular events. It was concluded that the negative predictive value of coronary artery calcium scores <10 could help classify patients with type 2 DM at a lower risk. In diabetes patients, the greater the coronary artery calcium score, the greater the all-cause mortality, compared to non-diabetic individuals, and the absence of calcium indicated a low risk of events.

Coronary calcium score in the reclassification of cardiovascular risk in type 2 diabetes mellitus

The presence of subclinical atherosclerosis was evaluated in a cohort study of 44,052 asymptomatic individuals, including 2,384 people with diabetes. Participants in the low and intermediate risk categories, with a coronary artery calcium score greater than 100, had mortality values of 39.4 deaths/1,000/, while those classified as high-risk, with a coronary artery calcium score = 0, had a mortality value of 6.59/1,000/year over a 10-year period. In the lower risk subgroup (< 5% in 10 years), 18% had a coronary artery calcium score > 100, while in the higher risk category (> 20% in 10 years), 16% had a coronary artery calcium score = 0. The use of the coronary artery calcium score reclassified a considerable number of low-risk patients into the high-risk category. A coronary artery calcium score > 0 was observed in 57.3% of the patients in the low -risk category and 70.6% in the intermediate risk category.[62]

Long-term studies such as The Coronary Artery Risk Development in Young Adults study prospectively evaluated 5,115 participants aged 18 to 30 years for the risk of developing CAD and cardiovascular events. The degree of CAC was assessed at 15, 20 and 25 years after recruitment. The probability of developing CAC, in the range of 32 to 56 years, was estimated using classic risk factors. Participants were followed-up for 12.5 years. After adjusting for risk factors and treatment, the presence of CAC was a risk predictor of CAD and CVD. The presence of CAC among individuals aged 32 to 46 years was associated with an increased risk of fatal and non-fatal CAD during 12.5 years of follow-up. Thus, screening for subclinical atherosclerosis, using the coronary artery calcium score, can be considered in individuals with risk factors in early adulthood for better risk discrimination.[63]

The MESA study evaluated the prevalence and progression of subclinical atherosclerosis in individuals without prior CVD. A total of 6,814 men and women aged 45 to 84 years were included, 9.8% of whom were diabetes patients, for the evaluation of the predictive power and improvement in the reclassification obtained by the addition of the CIMT coronary artery calcium score and the CIMT to the clinical risk score in the stratification of cardiovascular risk. The addition of the coronary artery calcium score to the Framingham global clinical score was superior in the risk stratification of CAD and CVD in diabetes patients with metabolic syndrome. The determination of the coronary artery calcium score had the best rates of risk reclassification when compared to the Framingham clinical global risk score and CIMT. This study observed that patients with diabetes have a variable risk spectrum, evidenced by the extent of CAC, noting that many diabetes patients do not necessarily present an equivalent risk of coronary disease.[64]

Carotid intima-media thickness and risk stratification in type 2 diabetes mellitus

CIMT, determined by carotid artery ultrasonography,[65] is a marker of cardiovascular events. In individuals older than 65 years, values greater than 11 mm are predictors of cardiovascular events.[66] Increases greater than 1 mm in the CIMT value are markers of CAD in younger individuals with no previous cardiovascular events.[67] Adding the CIMT measurement to the FRS modestly improved (7.6% p <0.001) the prediction of cardiovascular event risk in diabetes patients with metabolic syndrome.[61] In patients with type 2 DM, a CIMT value higher than 1.9 mm was a predictor of CAD, improving risk stratification when associated to the Framingham and UKPDS clinical scores in the Japanese population.[68]

In asymptomatic patients with type 2 DM, a sum greater than 1.1 mm in terms of the maximum plaque thickness on both sides of the carotid wall increases its predictive value for the detection of coronary stenosis by more than 50% (obstructive CAD), seemingly irrespective of age, hypertension, hyperlipidemia and HbA1c.[69]

Thus, new risk markers should stratify or reclassify patients to guide therapeutic decisions. Currently, the evaluation of subclinical atherosclerosis by imaging methods such as the coronary artery calcium score has the potential to identify individual risk in a personalized manner. These methods can improve the discrimination and reclassification of cardiovascular risk. There are huge implications in choosing risk assessment strategies. No intervention in primary prevention is free of costs or risks. The decision to use aspirin or statin in treatment is a long-term commitment to patients; this treatment course is efficient and cost-effective, but also has potential side effects. Risk stratification by a precise method that visualizes and quantifies the presence of calcium in the artery walls, by the calcium score, may help in the identification of cases in which the risk-benefit equation is favorable, and also those with damage from therapy (for example, those with a coronary artery calcium score = 0).

In this context, the Brazilian Evidence-Based Guideline on the prevention of CVD in patients with diabetes[6] recommends the following regarding the use of the coronary artery calcium score in the risk stratification of patients with DM: "The determination of the coronary artery calcium score has the best risk reclassification rates, when compared to other markers, when added to the overall risk score. This may be especially useful for reclassifying Intermediate Risk patients into Higher or Lower Risk categories. However, this panel recognizes that, despite its usefulness, the coronary artery calcium score is not an easily accessible examination for a large proportion of patients. [IIa, B]"

CVD is the main cause of morbidity and mortality in diabetes patients. Diabetes increases the risk of myocardial infarction, congestive heart failure, peripheral arterial disease, stroke, and mortality.

This increase in risk is related to the development of atherosclerosis of a greater severity. The more precocious it is and with more extensive progression, atherosclerosis in diabetes patients often affects smaller and more distal vessels, characterized by plaques with lipid content and a bulky necrotic nucleus, with a high infiltration of macrophages and T lymphocytes, forming inflamed plaques with greater vulnerability.

This difference in the cardiovascular risk associated with diabetes is also related to the intensity and multiplicity of the associated risk factors. As in the combined effect of diabetes-associated dyslipidemia in coronary atherosclerosis, qualitative abnormalities in LDL-c levels lead to the formation of small, dense particles that are more susceptible to oxidation and are, therefore, more atherogenic, as well as higher levels of triglycerides and lower levels of HDL-c. Thus, the correction of dyslipidemia, especially through reductions in the LDL-c levels, may have a greater benefit and impact in reducing CVD risk in diabetes patients.

Current evidence points to a need to intensify treatment aimed at reducing cardiovascular risk in diabetes patients. Optimized control of glycemic levels, especially with GLP1 receptor agonists and SGLT2 inhibitors; achievement of LDL-c goals, recommended according to individual risk stratification, with statins, ezetimibe and PCSK9 inhibitors; adequate control of pressure levels with drugs that contemplate metabolic protection; special attention to microalbuminuria; strict combat against smoking; and the use of anti-platelet therapy for patients at a higher risk are the most cost-effective interventions in the attempt to provide greater cardiovascular protection to diabetes patients.

However, although cardiovascular risk is increased in patients with diabetes compared to those without, recent evidence indicates that there is a high prevalence of low-risk individuals among this population. Thus, risk stratification is necessary either to intensify the effectiveness of preventive measures in the high-risk categories or to avoid over-treatment in patients in the low-risk category.

This type of risk-based approach aims to assist clinicians, endocrinologists, and cardiologists in the improvement of CVD prevention in patients with diabetes. We used the concept of treatment based on the achievement of statin intensity and the lipid target, because it is considered important in promoting better adherence and due to its utility in providing better prevention in DM patients. There is a clear trend towards the provision of high-intensity treatment for those in very high-risk categories, especially regarding lipid-lowering therapy with statins, in which the proposed lipid targets require such measures for the achievement of strict goals. It is understood that patients with diabetes at a very high risk have high mortality, and reductions of LDL-c levels are one of the most important actions currently available to reduce the residual risk. While the costs associated with the use of high-intensity treatment are high, their use can saves lives and help prevent health events, thus making up for the costs. The recommendations of the SBC, SBD and SBEM[6] fulfill the task of reducing CVD occurrence in patients with diabetes.

CONCLUSION

Diabetes is a heterogeneous disease that, although associated with increased CVD risk in most patients, may be associated with a lower risk in those individuals with no events, no risk factors, or no evidence of subclinical atherosclerosis. An optimized approach should be adopted to prevent CVD occurrence in high-risk individuals, while avoiding over-exposure to treatment among those at a lower risk. Therefore, prevention strategies should be individualized according to CVD risk, while treatment intensification should have a greater focus on those exposed to greater risks.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

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