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Most of the patients presenting myocardial infarction would not be eligible for intensive lipid-lowering based on clinical algorithms or plasma C-reactive protein

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ABSTRACT

Objective: The study we assessed how often patients who are manifesting a myocardial infarction (MI) would not be considered candidates for intensive lipid-lowering therapy based on the current guidelines.
Methods: In 355 consecutive patients manifesting ST elevation MI (STEMI), admission plasma C-reactive protein (CRP) was measured and Framingham risk score (FRS), PROCAM risk score, Reynolds risk score, ASSIGN risk score, QRISK, and SCORE algorithms were applied. Cardiac computed tomography and carotid ultrasound were performed to assess the coronary artery calcium score (CAC), carotid intima-media thickness (cIMT) and the presence of carotid plaques.
Results: Less than 50% of STEMI patients would be identified as having high risk before the event by any of these algorithms. With the exception of FRS (9%), all other algorithms would assign low risk to about half of the enrolled patients. Plasma CRP was <1.0 mg/L in 70% and >2 mg/L in 14% of the patients. The average cIMT was 0.8 ± 0.2 mm and only in 24% of patients was $\geq$1.0 mm. Carotid plaques were found in 74% of patients. CAC $\geq$100 was found in 66% of patients. Adding CAC $\geq$100 plus the presence of carotid plaque, a high-risk condition would be identified in 100% of the patients using any of the above mentioned algorithms.
Conclusion: More than half of patients manifesting STEMI would not be considered as candidates for intensive preventive therapy by the current clinical algorithms. The addition of anatomical parameters such as CAC and the presence of carotid plaques can substantially reduce the CVD risk underestimation.

1. Introduction

Clinicians have been concerned with how to assign properly the risk of cardiovascular disease (CVD) in the setting of targets for primary prevention. Indeed, recently, a significant reduction in CVD mortality was obtained by intensive lipid-lowering treatment in individuals a priori not considered candidates for such therapy according to the traditional risk estimation and to current guidelines [1]. In that trial, the use of elevated levels of C-reactive protein (CRP) as inclusion criterion could have helped to select patients at enhanced risk. However, the study design did not allow to verify if individuals who were not enrolled because of their low CRP were indeed at low risk or whether they could benefit or not from the same statin therapy.

More to the point, can the use of algorithms, markers of systemic inflammation or assessment of subclinical atherosclerosis mislead to a low CVD risk stratification and preclude patients from preventive therapies? And if so, how often this occurs? In order to probe this issue, in this study we assessed how often patients who are manifesting a myocardial infarction (MI) would not be considered candidates for intensive lipid-lowering therapy based on the current approach.

2. Methods

Study subjects were participants in the ongoing Brasilia heart study described elsewhere [2]. Briefly, in this prospective cohort, 355 consecutive patients admitted in the Hospital de Base, Brasília, Brazil, with ST-segment elevation MI (STEMI) were included in the study as of May 2006. Inclusion criteria were as follows: (i) less than 24 h after the onset of MI symptoms, (ii) ST-segment elevation of a least 1 mm (frontal plane) or 2 mm (horizontal plane) in

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two contiguous leads, and (iii) myocardial necrosis, as evidenced by increased creatine kinase–MB (CK–MB) and troponin levels. The study was approved by the Institutional Ethics Committee, and all patients signed an informed consent.

Medical evaluation and blood sampling were performed thereupon the admission at emergency department. The following measurements were performed: blood glucose (glucose GOD-PAP, Roche Diagnostics, Mannheim, Germany), total cholesterol (CHOD-PAP, Roche Diagnostics, Mannheim, Germany), triglycerides (GPO-PAP, Roche Diagnostics, Mannheim, Germany), HDL cholesterol (HDL cholesterol without sample pre-treatment, Roche Diagnostics, Mannheim, Germany), CRP (high-sensitivity CRP, Cardiophase, Dade Behring, Marburg, Germany). LDL cholesterol was calculated by the Friedewald formula.

The predicted CVD risk was estimated by the Framingham Risk Score (FRS) [3], the Prospective Cardiovascular Münster risk score (PROCAM) [4], the Reynolds risk score [5,6], the Assessing Cardiovascular Risk to Scottish Intercollegiate Guidelines Network/SIGN to Assign Preventative Treatment (ASSIGN) [7], and by the QRESEARCH cardiovascular risk algorithm (QRISK) [8,9]. According to these algorithms CVD risk was divided into three categories: low (<10%), intermediate (10–20%) and high (>20%) risk for an acute coronary event within the next 10 years. We also applied the Systematic COronary Risk Evaluation (SCORE) system from the European Society of Cardiology, which estimates the 10-year risk of a first fatal atherosclerotic event, whether heart attack, stroke, aneurysm of the aorta, or other [10]. For the SCORE, individuals with >5% of 10-year risk was considered as high risk [10].

Cardiac computed tomography (CT) and carotid ultrasound were performed in the following two weeks after hospital discharge. A 16-channel multidetector CT (1.5 mm slice thickness; Brilliance CT, Philips Healthcare, Cleveland, OH, USA) was used to calculate the coronary artery calcium score (CAC). The carotid intima-media thickness (cIMT) and the presence of plaques were studied using a high-resolution B-mode ultrasound (Philips, model IE 33, 3–9 MHz linear transducer, Philips, Andover, Massachusetts, USA) and a program of automatic edge detection (QLAB, Advanced Ultrasound Quantification Software, Release 7.1, Philips, Bothell, WA) according to the American Society of Echocardiography's guidelines [11]. Carotid plaque was defined as the presence of focal wall thickening that is at least 50% greater than that of the surrounding vessel wall or as a focal region with cIMT greater than 1.5 mm.

Data are presented as mean ± standard deviation for normally distributed data or median (25–75% percentiles) for skewed data. A two-sided p-value of 0.05 was considered statistically significant. Statistical analyses were performed using SPSS for Windows version 15.0. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

3. Results

Table 1 shows the clinical characteristics of the study participants. As Table 2, less than 50% of patients admitted with STEMI would be identified before the event as having high risk by any of these algorithms. The agreement between the algorithms for identifying patients as at high risk was low (kappa 0.11–0.50), suggesting that the parameters used in these scores can be complementary in identifying risk. In fact, 72% of patients would be identified as high risk by at least one of the seven risk scores. While the FRS was less equivocal in assigning low risk, other algorithms could ascribe it to more than 50% of the enrolled patients.

The time from MI symptoms onset and admission at the emergency department was 211 ± 253 min. Thus, in 77% of enrolled patients, blood samples were collected before the raise of CRP that normally occurs after 6 h of MI. In this blood testing, 70% of the patients had CRP <1.0 mg/L. Using CRP ≥2 mg/L as high risk defining criterion, only 14% of the patients would be eligible for intensive lipid-lowering therapy before the coronary event. There was no correlation between CRP and CAC or cIMT.

Table 1
Clinical characteristics of enrolled patients.

n	355
Men	75%
Age, years	61 ± 11
Hypertension	58%
Smoking	37%
Sedentary lifestyle	56%
Familial history of coronary disease	36%
Body mass index, kg/m^2	26 (24–30)
Waist circumference, cm	96 (91–103)
CRP, mg/L	0.5 (0.3–1.2)
LDL cholesterol, mg/dL	126 ± 46
HDL cholesterol, mg/dL	39 ± 11
Triglycerides, mg/dL	160 ± 122

In the evaluation after hospital discharge, the average cIMT was 0.8 ± 0.2 mm and only 24% of patients had cIMT ≥1.0 mm. No patient had cIMT above the 75th percentile for his or her age. Carotid plaques were found in 74% of patients. Adding the presence of carotid plaque data to the algorithms, a high-risk condition would be identified in 75% of patients by FRS, 77% by RRS, 81% by PROCAM, 80% by QRISK, 88% by ASSIGN and 74% by SCORE.

The CAC ≥100 or ≥400 were found in 66% and 29% of patients, respectively. However, in 17% of the participants, the reperfusion treatment was primary angioplasty with stenting. In such cases, the region bounded to the stent was removed from the analysis of CAC. As in 34% of these culprit lesions we observed calcification in the angiography before stenting, the CAC was underestimated in 20 cases (5.6%). Adding CAC ≥100 to the algorithms, a high-risk condition would be identified in 66% of patients by FRS, 68% by RRS, 74% by PROCAM, 76% by QRISK, 92% by ASSIGN and 66% by SCORE. Adding CAC ≥100 plus the presence of carotid plaque, a high-risk condition would be identified in 100% of the patients using any of the above mentioned algorithms.

4. Discussion

This study was not designed to validate methods for detection of CVD risk, but instead to verify the frequency of individuals at very high risk who are at the present erroneously underestimated and precluded from an intensive lipid-lowering therapy. In this context, we observed that more than half the patients with STEMI are not identified as high risk by the most well-established clinical algorithms. More serious than this, with the exception of FRS, about

Table 2
CVD risk according to clinical risk score algorithms.

Risk scores	CVD risk		
	Low	Intermediate	High
FRS, %	9	85	6
RRS, %	52	32	16
PROCAM, %	45	30	25
ASSIGN, %	72	21	8
QRISK, %	41	31	28
SCORE high risk chart, %	59	–	41
SCORE low risk chart, %	59	–	41

FRS: Framingham risk score; RRS: Reynold's risk score; PROCAM: prospective cardiovascular Münster risk score; ASSIGN: assessing cardiovascular risk to Scottish Intercollegiate Guidelines Network/SIGN to assign preventative treatment; QRISK: QRESEARCH cardiovascular risk algorithm; SCORE: Systematic COronary Risk Evaluation.

half of these individuals would be identified as low risk by the all algorithms. We also found that the addition of CAC ≥100 and presence of carotid plaques as high-risk criteria to the algorithms would substantially reduce the number of patients misclassified.

It's countless the number of modifiable factors, known and yet to be discovered, which may accentuate or attenuate the CVD risk. Therefore, it is not surprising that algorithms vary their efficacy in different populations. Even within the same population, the time and change of habits must modify the effectiveness of the algorithms. For example, algorithms developed in the 1970s and 1980s did not estimate adequately the impact of metabolic syndrome, an epidemic of today. In some years, the intensity of air pollution could become an important variable for the future algorithms [12]. In other words, the set of causes that promote atherogenesis vary dynamically and, thus, the actual risk can hardly be predicted by the same equation or algorithm in different circumstances, locations or over time.

In this study, we tested algorithms among the most frequently used around the world and noticed that none of these could identify as high risk half of patients admitted with STEMI. The low agreement and complementarity between them suggests the possibility of improving the representativeness and make them useful to a larger number of individuals. Indeed, new elements such as social deprivation, family history of CVD and body mass index were added by the QRISK [8,9] and ASSIGN [7] scores and reduced the number unidentified high risk patients in our study.

As noted, low values of plasma CRP and cIMT were found in three quarters of the patients enrolled into the study. This finding emphasizes the weakness in providing indicators of low risk in such a complex web of causation such as CVD. In contrast, the presence of atherosclerotic plaques in carotid or coronary arteries, the last as estimated by the CAC, was the more frequent finding among patients. Naturally, in agreement with other studies [13,14], the diagnosis of the disease overcomes the challenging of finding the components of the CVD causal chain and as well the limitations of the use of indirect unspecific markers such as CRP.

Some limitations must be considered when interpreting these findings. As 23% of patients arrived with more than 6 h of symptom onset, it is possible that a larger number of participants have had CRP <0.1 mg/L before the MI. As mentioned above, 17% of patients were treated by primary angioplasty with stenting and, therefore, the region around the stent was systematically removed for analysis of CAC. Thus it is probable that more than 66% of patients had CAC ≥100 before the coronary event. In this study, only 5% of patients enrolled were in prior use of statins and findings can be quite distinct in another setting. The CAC, for example, does not change significantly after treatment with statins, although it is known that atherogenicity, phenotype and CVD risk change [15]. Thus, any extrapolation from these findings must be carefully considered. Acquisition of CAC and carotid ultrasound was done about two weeks after the acute event and, although unlikely, we cannot assure you that there has been no progression of the atherosclerotic burden in coronary and carotid arteries detectable by these methods. Finally, as mentioned above, this study should not be considered as a validation of diagnostic methods for cardiovascular risk. Rather, this serves to draw attention to the dramatic number of individuals currently classified as having low or intermediate risk for cardiovascular disease and who are consequently deprived of an intensive prevention strategy. For the individuals enrolled in this study, assessment of subclinical atherosclerosis would have made a difference.

In conclusion, the present study showed that based on the current strategy for identifying CVD risk, more than half of patients admitted with STEMI would not be considered candidates for intensive preventive therapy before the event. In addition, consistently with previous studies, this study suggest that the complementation of clinical algorithms with of anatomical parameters such as CAC and the presence of carotid plaques can substantially reduce the underestimation of CVD risk.

Disclosures

The authors state that they have no conflict of interest.

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