FULL LENGTH ARTICLE

Quantifying the impact of using Coronary Artery Calcium Score for risk categorization instead of Framingham Score or European Heart SCORE in lipid lowering algorithms in a Middle Eastern population

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Background: **The use of the Coronary Artery Calcium Score (CACS) for risk categorization instead of the Framingham Risk Score (FRS) or European Heart SCORE (EHS) to improve classification of individuals is well documented. However, the impact of reclassifying individuals using CACS on initiating lipid lowering therapy is not well understood. We aimed to determine the percentage of individuals not requiring lipid lowering therapy as per the FRS and EHS models but are found to require it using CACS and vice versa; and to determine the level of agreement between CACS, FRS and EHS based models.**

Methods: **Data was collected for 500 consecutive patients who had already undergone CACS. However, only 242 patients met the inclusion criteria and were included in the analysis. Risk stratification comparisons were conducted according to CACS, FRS, and EHS, and the agreement (Kappa) between them was calculated.**

Results: **In accordance with the models, 79.7% to 81.5% of high-risk individuals were down-classified by CACS, while 6.8% to 7.6% of individuals at intermediate risk were up-classified to high risk by CACS, with slight to moderate agreement. Moreover, CACS recommended treatment to 5.7% and 5.8% of subjects untreated according to European and Canadian guidelines, respectively; whereas 75.2% to 81.2% of those treated in line with the guidelines would not be treated based on CACS.**

Conclusion: **In this simulation, using CACS for risk categorization warrants lipid lowering treatment for 5–6% and spares 70–80% from treatment in accordance with the guidelines. Current strong evidence from double**

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randomized clinical trials is in support of guideline recommendations. Our results call for a prospective trial to explore the benefits/risks of a CACS-based approach before any recommendations can be made.

Keywords: Coronary Artery Calcium Score, Lipid lowering therapy, Reclassification, Risk categorization, Canadian Cardiology Society guidelines, European Society of Cardiology guidelines

Introduction

The Coronary Artery Calcium Score (CACS), measured in Agatston units (AU), is a non-invasive method of measuring calcification in the coronary arteries [1]. It is used to assess the overall coronary calcified plaque burden thereby providing prognostic information regarding the occurrence of future cardiovascular (CV) events [2,3]. A high CACS indicates that individuals are at high risk for cardiovascular events even if they were classified as having low or intermediate risk using traditional risk assessment tools such as the Framingham risk score (FRS), as adopted by the Canadian Cardiology Society (CCS) [4], or the European Heart SCORE (EHS) [5]. These individuals may necessitate aggressive preventive lipid lowering therapy [6].

Historically, incorporating the traditional CV risk factors such as blood pressure, age, gender, smoking, and cholesterol levels into the FRS and EHS models aided clinicians in risk classification and in decisions on initiating therapeutics [5]. However, experience – supported by various studies – has demonstrated the shortcomings of these models in predicting coronary heart disease (CHD) [7,8]. CACS has become a well-established surrogate marker of coronary atherosclerosis [9]. Despite the fact that the mechanism underlying CAC deposition within atherosclerotic plaque is not yet entirely clear, CAC has been shown in autopsy studies to significantly correlate with the overall coronary tree plaque burden [10]. Improvement in CHD risk prediction using CACS in comparison to traditional risk factors is well documented. Five major studies have significantly and favorably influenced the opinions of scientific communities on the usefulness of CACS as a predictor of events. These are the Multi-Ethnic Study of Atherosclerosis (MESA) [11], the Heinz Nixdorf Recall (HNR) study [12], the Rotterdam study [13], the JUPITER-MESA study [14], and the publications from the CONFIRM Registry [15]. These studies showed that CACS is an independent predictor for CHD [16] and has added value over the FRS tool in that it performs similarly in multiple ethnicities and works well in both women and men. Currently, the AHA categorizes CAC scoring as a Class 2B recommendation among asymptomatic persons at intermediate risk for cardiac events by the FRS tool [17].

Abbreviations

AU	Agatston units
CACS	Coronary Artery Calcium Score
CCS	Canadian Cardiology Society
CHD	Coronary Heart Disease
CV	Cardiovascular
EHS	European Heart SCORE
ESC	European Society of Cardiology
FRS	Framingham Risk Score
NRI	Net Reclassification Index

The clinical utilization of CACS has been validated in several areas, with varying levels of evidence in the area of reclassifying an individual's risk for CHD events and in improving adherence with preventive therapeutic recommendations. Recent evidence suggests that reclassification of patients from intermediate risk as per Framingham risk score to high-risk status based on CACS warrants aggressive preventive therapy, especially as treatment decisions for this group are indecisive [2]. However, no evidence-based guidelines currently exist on how to implement CACS risk categorization in treatment algorithms. The utilization of CACS for risk stratification is gaining wide acceptance [18], and appears to impact both the patient at the individual level and the healthcare system at large. Whereas the net reclassification index is the most consulted measure in the literature, the initiation of therapeutics amongst all up-classified individuals remains a current practice. This may be justified since there is no proof that intensive preventive interventions can be safely reduced in persons at high Framingham risk and low risk by CACS [13]. Hence, quantifying the impact of up and down-classification on initiating therapeutics will enable improved clarification of the cost–benefits to CACS utilization [19].

In this study, we aim first to determine the percentage of individuals not requiring lipid-lowering therapy as per FRS and EHS models but who are found to require lipid-lowering interventions using CACS, and to quantify the opposite scenario. Second, we aim to determine the level of agreement between the CACS method of CV risk classification and the FRS and EHS models.

Methods

This is a cross-sectional study within a nested cohort of patients who have already undergone CAC scoring. The cohort was identified through an interrogation of the Imaging Storage Digital system. A retrospective chart review for 500 consecutive patients included collection of data on patients' medical history of co-morbidities including diabetes, hypertension, dyslipidemia, and family history of CAD and cardiovascular event occurrence. Data collected also included medications received, blood test results including lipid profile and fasting blood sugar, heart rate and blood pressure measurement, and lifestyle habits including smoking. This study was approved by the institutional review board at the American University of Beirut. A total of 242 patients eligible for the study were included in the analysis. Exclusion criteria included patients with type 2 diabetes mellitus (DM), aged 40 years or less, already on statin treatment or other lipid lowering therapy, having a history of coronary artery bypass grafting before the CT scan, having significant stenosis (defined as more or equal to 50% stenosis by the CT coronary angiography) or having undergone percutaneous coronary intervention (balloon dilatation or stent deployment) in one of the coronary arteries. These patients were excluded as they were already categorized as high risk and CAC scoring for the purpose of lipid lowering is not warranted. As for type 2 diabetic patients, they were excluded because recommendations to initiate lipid lowering are different from the general population in being not dependent on FRS or EHS models. In brief, the group we chose to include is dependent on FRS or EHS models for determining subsequent lipid therapy.

Definitions of terms used

Family history of CAD was defined as any direct blood relatives (parents, siblings, or children) who have had acute myocardial infarction or sudden cardiac death without obvious cause, coronary artery bypass graft surgery, or percutaneous coronary intervention at an age less than 55 years for male relatives or less than 65 years for female relatives [20,21].

Hypertension was defined by three criteria, where having either one would make the subject a positive case. The criteria included having a history of hypertension diagnosed and treated with medication, diet and/or exercise. The second was prior documentation of blood pressure greater than 140 mm Hg systolic and/or 90 mm Hg diastolic for patients without diabetes or chronic kidney disease. The third was prior documentation of blood pressure greater than 130 mm Hg systolic and/or 80 mm Hg diastolic on at least two occasions for patients with diabetes or chronic kidney disease [22].

Type 2 diabetes mellitus was defined as any occurrence of Hemoglobin A1c (HbA1C) $\geqslant$6.5 or Fasting blood sugar (FBS) $\geqslant$126 mg/dL in laboratory tests or documentation of DM 2 by the treating physician. Current or recent smoking indicates if the patient had smoked cigarettes anytime during the month prior to arrival at our facility.

Identifying a positive dyslipidemia case was based on the National Cholesterol Education Program criteria and included documentation of a total cholesterol greater than 200 mg/dL (5.18 mmol/l), low-density lipoprotein (LDL) greater than or equal to 130 mg/dL (3.37 mmol/l); high-density lipoprotein (HDL) less than 40 mg/dL (1.04 mmol/l) [23]. Moreover, patients on treatment for hypercholesterolemia with statins or Ezetimibe were considered to have dyslipidemia.

Risk classification of patients

The CCS Guidelines categorize patients into low (FRS <10%), intermediate (10% < FRS <20%), and a high (FRS >20%) 10-year risk of developing cardiovascular (CV) disease [20,24].

Similarly, using EHS, the 10-year risk for CV death was calculated. Thereafter, patients were classified into low (<1%), intermediate (1–5%), and high (>5%) 10-year risk for CV death, and based on the European Society of Cardiology (ESC) guidelines, the downstream treatment indications were determined [25].

Finally, using CACS, patients were categorized into low (<100 AU), intermediate (100–399 AU) and high (>400 AU) 10-year CV event rate [26]. Subsequently, this risk categorization was inserted instead of the risk categorization by the FRS and EHS in their corresponding algorithms, and thereafter downstream treatment indications were derived.

The use of these cut-points is based on the American College of Cardiology/American Heart

Association (ACC/AHA) 2007 clinical expert consensus document on coronary artery calcium scoring. It was found that the estimated annual risk of CHD death or myocardial infarction (MI) rates to be ''0.4%, 1.3%, and 2.4% for each tertile of CAC score where scores ranged from less than 100, 100 to 399, and greater than or equal to 400, respectively'' [27]. A simplified approach would permit the assumption that when projected for 10-year rates, 4% is below the 10% cutoff for 10-year risk, that is, low risk; 13% is below the 20% cutoff for the 10-year risk, that is, intermediate risk; and 24% is above the high-risk cutoff. Hence, the strata for comparison of different treatment guidelines are based on prognosis according to CACS, which approximates the same prognostic meaning as the strata according to EHS or FRS. This can be further justified according to the FinRISK study that suggests the total event rate is 15% at the risk management advice level of 5% at which it is likely to be intensified [25].

Determination of lipid lowering treatment

FRS was calculated based on the original formula set by the Framingham study [28]. The treatment algorithm followed to determine need and type of treatment of dyslipidemia was as per the CCS guidelines [4].

Statistical analysis

Continuous and categorical variables were described as means ± standard deviation or counts and percentages, respectively. Comparisons between groups were done using independent t-test for continuous variables, and Chi-square test or Fisher's Exact Test, as applicable, for categorical ones. Agreement between the different risk scoring systems was calculated based on weighted Kappa coefficients. A value between 0.01 and 0.2 represents slight agreement and a value between 0.21 and 0.4 represents fair agreement [29]. Framingham and European risk scores were calculated using SigmaPlot 11.0 software (Systat Software Inc., San Jose, Calif.). Analyses were performed using SPSS version 20.0 (IBM, USA) and STATA 13.0 software. A p value of $\leqslant 0.05$ was used to indicate significance of tests.

CAC acquisition

All CACS examinations were performed on a 64-slice CT scanner (Sensation 64; Siemens Healthcare, Forchheim, Germany). The scanner had a gantry rotation time of 300 milliseconds and a detector row width of 0.6 mm. The scanner acquired 64 incremental 3-mm slices with prospective ECG-gating and a flying focus along the z-axis, covering 2 cm below the carina to the level of the diaphragm (z-sharp technology; Siemens Healthcare). The scanner's temporal resolution was 75 milliseconds; pitch 3.4; effective mA 80 and tube voltage 120 kVp. Volume CT dose index and dose length product (DLP) per scan were recorded from the scanner console. Effective dose was obtained by multiplying the DLP of the scan by a constant factor for the chest per European Commission guidelines on quality criteria on CT (k 5 0.014 mSv * mGy21 * cm^2). CAC scoring was performed by the Agatston method [26].

Results

Baseline characteristics of the cohort are displayed in Table 1. Of the 242 eligible participants, 115 (52.5%) patients had a Coronary Artery Calcium Score of zero. Gender differences were significant in terms of age, total and HDL cholesterol, Agatston Coronary Artery Calcium score, Framingham risk score, and European Heart SCORE. Females had significantly higher mean total cholesterol (209.3 ± 35.0 mg/dL; $p = 0.05$), higher mean HDL cholesterol (59.4 ± 18.0 mg/dL; $p < 0.01$), and higher mean age (58.9 ± 9.3 years; $p < 0.01$). Males had higher CAC score (173.9 ± 476.6AU; $p < 0.01$), and higher risk of cardiovascular disease (CVD) as per percent FRS (17.0 ± 12.7%; $p < 0.01$), and percent EHS (5.2 ± 9.7%; $p < 0.01$).

Of the 242 patients, 38.0% were classified as having intermediate risk as per FRS, of whom 7.6% and 77.2% were found to be at high risk and low risk using CAC score, respectively. Moreover, a slight agreement level (kappa = 0.143; $p < 0.01$) between the two risk assessment tools was calculated. This low level of agreement was present in both genders (Tables 2A, B).

On the other hand, as per the EHS, 48.8% of patients were classified as intermediate risk. Of this group, 6.8% and 83.1% were found to be at high risk and low risk using the CAC score categorization. Again, a slight agreement level (kappa = 0.087; $p < 0.01$) between the two risk assessment tools was calculated (Tables 3A, B). Analysis of FRS risk score on patients with a CAC score of zero showed that 10.4% had high FRS risk while 34.8% had intermediate risk.

The impact of reclassification was demonstrated in treatment recommendation discrepancies between the CCS guidelines using the FRS and CAC score and between the ESC guidelines

Table 1. Baseline characteristics of the study population across gender and age groups.

Variable	All (N = 242)	Male (N = 169)	Female (N = 73)	p-value	<=50 y.o. (N = 84)	50–65 y.o. (N = 136)	>65 y.o. (N = 57)	p-value
Continuous variables (Mean ± SD)								
Age (years)	56.0 ± 10.0	55.2 ± 10.1	58.9 ± 9.3	<0.01				
Body mass index (kg/m^2)	31.6 ± 27.5	33.5 ± 33.1	27.6 ± 5.7	>0.05	28.9 ± 4.8	34.1 ± 38.8	29.6 ± 6.0	>0.05
Systolic blood pressure (mmHg)	129.9 ± 18.1	131.0 ± 16.3	127.2 ± 21.5	>0.05	130.3 ± 17.8	128.3 ± 17.1	133.0 ± 20.8	>0.05
Total cholesterol (mg/dl)	197 ± 63.0	192.3 ± 71.0	209.3 ± 35.0	0.05	201.0 ± 46.0	199.0 ± 79.0	188.0 ± 43.0	>0.05
LDL cholesterol (mg/dl)	120.0 ± 36.0	117.9 ± 36.0	124.7 ± 35.0	>0.05	128.0 ± 38.0	117.0 ± 31.0	111.0 ± 38.0	<0.05 $^{\pi}$
HDL cholesterol (mg/dl)	50.0 ± 17.0	45.4 ± 14.0	59.4 ± 18.0	<0.01	46.0 ± 19.02	51.0 ± 15.0	53.0 ± 15.0	>0.05
Triglycerides	138.0 ± 107.0	142.8 ± 120.0	128.0 ± 70.0	>0.05	161.6 ± 146.0	127.0 ± 86.0	126.0 ±58.0	>0.05
Calcium score (AU)	137.7 ± 412.9	173.9 ± 476.6	53.7 ± 174.5	<0.01	136.8 ± 51.6	141.5 ± 430.2	359.1 ± 615.1	<0.01 $^{\pi,¥}$
Framingham Risk Score (%)	14.8 ± 11.7	17.0 ± 12.7	9.6 ± 6.4	<0.01	10.1 ± 6.6	14.6 ± 10.8	24.0 ± 15.5	<0.01 *
European Heart Score (%)	4.4 ± 8.4	5.2 ± 9.7	2.5 ± 3.1	<0.01	1.4 ± 1.3	4.1 ± 9.6	10.5 ± 9.4	<0.01 $^{\pi,¥}$
Categorical variables (%)								
Age								
⩽50 y.o.	34.7	41.4$^{\Omega}$	19.2$^{\Omega}$	<0.01				
50–65 y.o.	46.7	42.0	57.5					
>65 y.o.	18.6	16.6	23.3					
Hypertension	35.1	37.3‡	30.1‡	>0.05	28.6	32.7	53.3	0.01
Antihypertensive medication	28.9	27.8‡	31.5‡	>0.05	22.6	27.4	44.4	<0.05
Dyslipidemia	36.4	36.7‡	35.6‡	>0.05	29.8	42.5	33.3	>0.05
Smokers	26.9	26.0‡	28.8‡	>0.05	31.0	24.8	24.4	>0.05
Family history of CAD	16.7	14.4‡	22.2‡	>0.05	19.3	17.0	11.4	>0.05
Non-Zero Calcium score	52.5	60.9‡	32.9‡	<0.01	31.0	59.3	75.6	<0.01

‡ % is within gender.
* all cases significant.
$^{\Omega}$ <=50 y.o. vs 50–65 y.o. significant.
$^{\pi}$ <=50 y.o. vs >65 y.o. significant.
$^{¥}$ 50–65 y.o. vs >65 y.o. significant.

Table 2. Risk categorization for total sample by Coronary Artery Calcium Score and (A) Framingham Risk Score (FRS) and (B) European Heart SCORE (EHS).

		CAC Score Based Risk Categorization			Agreement Level Kappa (*p*-value)
		Low (0–99) *N* (%)	Intermediate (100–399) *N* (%)	High (⩾400) *N* (%)	
(A)					
FRS Based Risk Categorization	Total (*N* = 242)				
	Low (<10%)	89 (91.8)	5 (5.2)	3 (3.1)	0.143 (<0.01)
	Intermediate (10–20%)	71 (77.2)	14 (15.2)	7 (7.6)	
	High (>20%)	34 (64.2)	8 (15.1)	11 (20.8)	
(B)					
EHS Based Risk Categorization	Total (*N* = 242)				
	Low (<1%)	57 (95.0)	3 (5.0)	0 (0.0)	0.087 (<0.01)
	Intermediate (1–5%)	98 (83.1)	12 (10.2)	8 (6.8)	
	High (>5%)	39 (60.9)	12 (18.8)	13 (20.3)	

Table 3. Stratification of treatment indication for total sample as per Coronary Artery Calcium Score (AU) versus (A) Canadian Cardiology Society (CCS) guidelines and (B) European Society of Cardiology (ESC) guidelines.

	Indication to treat as per CCS guidelines using CACS risk categorization			Agreement Level Kappa (*p*-value)
		No *N* (%)	Yes *N* (%)	
(A)				
CCS guidelines indication to treat	Total (*N* = 242)			
	No	129 (94.2)	8 (5.8)	0.205 (<0.01)
	Yes	79 (75.2)	26 (24.8)	
(B)				
ESC guidelines indication to treat	Total (*N* = 242)			
	No	83 (94.3)	5 (5.7)	0.102 (<0.01)
	Yes	125 (81.2)	29 (18.8)	

utilizing EHS and CAC score. Of the 242 subjects, CAC score-based algorithms recommended preventive lipid lowering treatment for 5.8% of patients who were not treated as per CCS and for 5.7% who were not treated as per ESC algorithms. Conversely, 75.2% and 81.2% of those who would qualify for treatment as per CCS and ESC guidelines, respectively, would not qualify when using CACS as a tool for risk categorization instead of the corresponding FRS and EHS systems, respectively. The agreement between CCS FRS based treatment and CCS CAC score-based treatment indications was slight (Kappa = 0.205; $p < 0.01$), similar to that between ESC EHS based treatment and ESC CAC score-based algorithms which was also slight (Kappa = 0.074; $p = 0.039$). Similar low levels of agreement were found across gender and age groups (Supplementary Tables S1–S4).

Discussion

Key findings

This study supports several observations. First, the majority of individuals classified as being at high risk as per the FRS were down-classified by CACS to intermediate (15.1%) and low risk (64.2%). Similarly, high risk individuals as per the EHS were down-classified by CACS to intermediate (15.2%) and low risk (77.2%). Second, of those at intermediate risk as per the FRS and EHS, 7.6% and 6.8%, respectively, were up-classified into high risk category as per CACS. Third, the downstream implication of using CAC score based categorization on recommending lipid lowering treatment was quantified, showing that this use will lead to recommending treatment to 5.8% and 5.7% of subjects who would have been left untreated according to CCS and ESC guidelines, respectively. Conversely, of those who would be treated by CCS and the ESC guidelines, 75.2% and 81.2%, respectively, would not be treated if risk categorization was based on CACS. These two latter observations were in turn reflected in the fourth finding where the level of agreement between FRS and CAC score based risk categorization, and between EHS and CAC score based risk categorization were both slight (kappa <0.21). Given the increasing adoption of CACS for risk assessment, and the conflicting downstream therapeutic choices noted from these observations, the implications of these findings

warrant further investigation. The evidence supporting current recommendations in the guidelines is based on randomized clinical trials. This study is a simulation within a retrospective design, and thus represents a call for a randomized trial to clarify the risks/benefits of such an approach.

Reclassification results in other studies and how they compare to ours

Results from our study show that a CAC score $\geqslant$400 AU was recorded in 5.7% of EHS-based intermediate risk patients and 5.8% of FRS-based intermediate risk patients; hence up-classifying them into the high risk category. Furthermore, 77.2% and 83.1% of intermediate risk individuals as per FRS and EHS, respectively, were found to have a CAC score <100, placing them in the low risk category. In fact, 43.5% of subjects with intermediate FRS had a CACS of zero. Accordingly, these subjects have a 3–5 year event rate of 0.4% suggesting an event rate of <0.1% [2]. In comparison, Okwuosa et al recorded the distribution of CACS by Framingham 10-Year Risk Strata in 5660 participants from the MESA cohort using three cutoff points; CACS >0, $\geqslant$100, and $\geqslant$300, and they found that 15.6% of individuals with FRS 10–15% and 24.1% of individuals with FRS 15.1–20% FRS, which comprises the intermediate risk group, had a CAC $\geqslant$300 AU, and therefore would be up-classified. They also found that 63.9% and 73.0% of individuals in their two intermediate risk groups had a CAC <100 AU, comprising low CV risk [30]. These observations render our results of up-classification of approximately 6% in the same range, though slightly lower in keeping with the higher cut-point used in this study. On the other hand, the cut-point used for low risk classification (CACS <100 AU) was the same in this study and that by Okwuosa et al, rendering the range of down-classification from the intermediate risk group to also be in the similar range. Similarly, data from Preis et al showed that 22% of intermediate CHD risk individuals had a CAC score $\geqslant$90th percentile (high risk as per this study). This percentage almost doubled to 39% when using Agatston score with an absolute CACS cut-point of 100 Hounsfield units [6]. While the utilization of the age–gender percentile cut-points for risk classification has been used by some authors, this trend did not appear to be of significant predictive value compared to absolute CAC. This has been shown in a study by Budoff et al, where absolute CAC performed better than age, sex, and race/ethnicity-specific percentiles in terms of model fit and discrimination. This was expressed with a higher area under the receiver–operating characteristic curve for absolute CAC compared to percentile (women: area under the curve (AUC) 0.76 versus 0.73, $p = 0.044$; men: AUC 0.77 versus 0.73, $p < 0.001$) [31].

Applicability of CVD prevention guidelines and downstream therapeutic implications

The limitations of the international applicability of guidelines in general have been highlighted by the World Health Organization (WHO) [32]. Furthermore, in a recent paper, significant discrepancies in applicability have been noted between guidelines for CVD prevention and recommended lipid lowering interventions when applied on a 'seemingly healthy' cohort of persons in particular [33]. Namely, the ESC 2012 guidelines [25] and the CCS 2012 guidelines [4] have shown substantial agreement (Kappa 0.77) for the entire cohort, but with much lower agreement (Kappa 0.63) when females are considered alone [33]. This underscores the weakness in the applicability of these guidelines among different ethnicities and between genders. Moreover, a special concern is underlined in countries where CVD incidence is on the rise, such as Middle Eastern countries in particular, where it is hypothesized that currently existing risk scoring systems may underestimate risk [25]. On the other hand, several studies have proven the accuracy of the CAC score in predicting CVD risk among different ethnicities and between genders [16,30,34]. Consequently, applying CACS in countries where no applicability studies for either the FRS or EHS have been performed will confer greater accuracy in risk estimation. This is further corroborated by studies that have demonstrated more refinement of event prediction by CACS based on the net reclassification index (NRI).

The accuracy of event prediction using CACS was demonstrated in the reclassification results from the Heinz Nixdorf Recall Study which showed an NRI of 21.7% of FRS-based intermediate risk subjects to low CAC score (<100) and 30.6% to high CAC $\geqslant$400 [12]. Furthermore, this result was replicated when Polonsky et al showed that by adding CACS to their prediction model, a net reclassification improvement of 25% (95% confidence interval, 16–34%; $p < 0.001$) from 5,878 healthy, non-diabetic individuals from the MESA cohort was obtained. Using CAC with the prediction model, approximately 8% were reclassified

into the highest or lowest risk categories compared to the prediction model by itself, which accounted for age, sex, tobacco use, systolic blood pressure, antihypertensive medication use, total and high-density lipoprotein cholesterol, and race/ethnicity. In addition, a 23% reclassification improvement was noted for those who experienced events and 13% for those who did not [35]. Along the same line, data from the Rotterdam Study also showed that in a cohort of 2,028 asymptomatic participants, 52% of intermediate risk participants based on a Framingham refitted risk model, were reclassified more accurately based on CAC score, using the cutoff point above 615 AU for high score and below 50 AU for low score [13]. All these results provide solid evidence for the cross-gender and cross-ethnic ability of CACS in risk stratification.

The implications of our results on downstream lipid-lowering initiation provide a quantitative assessment to the impact of using CACS for risk categorization. Our results show that CAC score based risk categorization recommended preventive lipid lowering treatment for 5.8% of patients who were not treated as per FRS-based CCS (Kappa = 0.205; $p < 0.01$) and for 5.7% who were not treated as per EHS (Kappa = 0.102; $p < 0.01$). Conversely, 75.2% and 81.2% of those who would qualify for treatment as per the CCS and ESC guidelines, respectively, would not qualify when using CACS as a tool for risk categorization. The low level of agreement noted in the downstream effects on initiating therapeutics carries serious concerns and opportunities. First, in countries where several systems are used, this is space for confusion in the healthcare system and among patients. Second, given that efforts to validate the EHS or FRS systems may be considered in certain countries, these results highlight the potential of an algorithm that utilizes CACS which can save time (waiting for prospective validation) and is more robust in predicting CV outcomes.

Third, all guidelines for prevention of CVD base their recommendations to initiate statins on CV risk categorization using either FRS or EHS, among other variables. This has led to an increase in the number of individuals receiving statins. The risks of statins tend to be accepted by physicians and patients. However, when results show that using a different risk scoring system between 70–80% of individuals can be spared this risk, this is not to be belittled. On the other hand, implementing a CAC scoring based strategy is also neither risk nor cost-free. Several researchers have highlighted concerns with radiation from CAC scoring [36,37]. This would be of more concern if repeated testing were to be recommended for follow up. While recent technological advances have led to the reduction of radiation doses [38], we are uncertain as to how many of the currently present machines in Lebanon or other parts of the Middle East use the new radiation limiting software. Furthermore, the cost of undergoing repeated CAC scoring is not to be underestimated. The introduction of cardiac CT angiography in general is reported to have increased downstream risk and cost [39]. The high exclusion rate in our cohort may suggest that this is also occurring in Lebanon. Furthermore, unfortunately, no studies from the Middle East region replicate these cost–benefit assessments to present a better assessment of the reality in our area. In this region, it is clearly the responsibility of governmental agencies to fund studies that can verify the benefits/hazards/outcomes of basing recommendations of lipid lowering on CACS versus FRS or EHS. The recommendations in the guidelines are based on double randomized clinical trials that have demonstrated clinical effectiveness of the currently widely accepted approach. Despite that, the proposed approach here can potentially lead to direct cost savings from not starting statins and indirect savings from preventing the side effects of the medications; and the benefits and risks of such an approach and its effectiveness compared to the current recommendations need to be ascertained in a randomized trial before any recommendations can be made. Of note, the Society for Heart Attack Prevention and Eradication (SHAPE) guidelines do incorporate a CACS based treatment algorithm. However, this algorithm is limited by a concern that it extrapolates the proven ability of CACS to classify risk into the practice of making therapeutic choices without sufficient evidence to support this, including clinical effectiveness or cost–benefit analyses [40].

Conclusion

In conclusion, this study has quantitatively suggested that the use of CACS for risk categorization instead of risk factor based systems such as the FRS or EHS, would significantly alter treatment recommendations. Around 6% of those not recommended lipid lowering therapy using risk factor based systems will be using CACS, and between 70% and 80% of those recommended lipid lowering therapy would be spared this treatment. This result was similar for both genders. The current

guidelines are supported by strong evidence from randomized trials. Our results are a simulation of a possible alternative path from a retrospective design and therefore constitute only a call for a future prospective study to explore the risks/benefits of such an approach.

This study is limited by its inherent design in being retrospective within a nested cohort. We excluded those with >50% stenosis, i.e., obstructive CAD, since these will normally proceed to invasive catheterization and will thereafter require intensive lipid lowering. Our design addresses the problem of patients with non-obstructive disease, or <50% stenosis. A potential source of error in risk prediction in patients with non-obstructive disease and a CACS rendering them at low risk is suggested by evidence from the literature describing non-calcified plaques and mixed plaques as bearing different outcomes. This may have occurred in our study and therefore limits the conclusions we have reached. However, data from the CONFIRM registry [15]. l have shown that the ability of CT coronary angiography to correctly reclassify individuals from models, including established risk categories based on the model with Framingham risk factors plus CACS, was limited. Furthermore, they found that the NRI from including CT coronary angiography data was particularly weak numerically for all-cause mortality, at $\leqslant 0.05$, and was modestly better for the composite outcome. Thus, we find it reasonable to use CACS only for CV risk categorization in the <50% stenosis group in particular. Another limitation in our study is the total number of individuals included. We admit that using this sample number to provide generalizations at a population level is not well-founded and we therefore recommend a larger study to validate our findings.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jsha.2015.05.004.

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