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Coronary Artery Disease Severity and Outcomes

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Abstract

Improved lifestyle, together with more effective pharmacotherapy and invasive treatment, has resulted in a decline in first-time coronary artery disease (CAD) and increased survival in patients with established CAD. Despite the decline in mortality from CAD, it remains one of the leading causes of premature death on a European scale. Aside from an additional risk of premature death, CAD is also associated with risk of recurrent cardiovascular events, e.g. stroke and recurrent myocardial infarction (MI), with the highest risk of recurrent events during the first year after MI. This risk is targeted by a similar guideline recommended treatment duration, but evidence has shown that the risk persists beyond the first year after MI and that risk depends on patient's risk profile. With projected increase in high-risk patients that stay event-free on first year after MI and associated long-term health-care burden, it has become even more relevant to clarify the long-term risk of recurrent events in stable post-MI patients with distinct risk profiles. Thus, high-risk patients might benefit from extended tailored treatment approach. However, it is important to highlight the fact that a considerable proportion of patients with established illness still appear to receive sub-optimal cardiac care, secondary prevention and cardiac rehabilitation. Another serious challenge is that prevalence of coexisting chronic illnesses, which in many cases share same risk factors as CAD, is high and increasing, but even more importantly, are associated with unfavorable prognosis in patients with CAD. Although CAD severity is one of the strongest risk factors for long-term outcome, its importance in late-risk stratification and in relation to co-morbidity among stable post-MI patient who have stayed event-free on first year is not entirely clear.

Keywords: Coronary Artery Disease, Severity, SYNTAX Score

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1. Methods of Assessing CAD Severity

1.1. Angiographic Techniques (e.g., SYNTAX Score)

The SYNTAX score was developed through expert consultation, and integrated previous angiographic scores that assessed lesion complexity: the AHA classification modified for the ARTS (Arterial Revascularization Therapy Study) study, the Leaman score, the ACC/AHA lesions classification system, the total occlusion classification system, and the Duke and ICPS classification systems for bifurcation lesions. Subsequently the Medina classification of bifurcation lesions was introduced [1]. The SYNTAX score was designed to quantify the complexity of left main (LM) or three-vessel disease. Using the openly accessible web based score calculator, it is possible to calculate each patient's SYNTAX score by answering a series of questions. The SYNTAX score corresponds to the lesion complexity measured by the coronary tree characteristics and the lesion locations and specifics**Error! Reference source not found.**. One of the most crucial features of the SYNTAX score is that it is a lesion based score, which integrates all lesions to determine the degree of myocardium that is at risk and the technical success rate of treating each lesion. Three general questions are asked, and for every lesion, eight questions need to be answered to determine the lesion's individual score, which accumulates to form the overall SYNTAX score of the patient [2].

1.1.1. The Syntax Score as a Prediction Tool

Initial validation of the SYNTAX score was accomplished by retrospective application to 1292 lesions in 306 patients who had undergone PCI for three vessel disease in the ARTS-II (Arterial Revascularization Therapies Study part II). Thirty day results showed a stepwise increase in major adverse cardiac or cerebrovascular events (MACCE) for patients with an increasing SYNTAX score from low (≤18) to intermediate (19–26) to high (≥26): 3% vs 5% vs 12% (p=0.03). This was mainly driven by periprocedural myocardial infarction (p=0.04) and target vessel revascularization (p=0.02). After a median follow-up of 370 days, patients with the SYNTAX scores ≥26 had significantly higher MACCE rates. Multivariate analyses showed that the raw the SYNTAX score was an independent predictor of MACCE (hazard ratio (HR) 1.07, 95% confidence interval (CI) 1.03 to 1.11) [3]. A number of studies have since evaluated the predictive power of the SYNTAX score in patients undergoing the PCI. It has repeatedly been identified as a strong independent predictor of death and the MACCE during long term follow-up. The data on the predictive ability of the SYNTAX score in patients undergoing the CABG have been conflicting. Although some reports have shown that the

SYNTAX score is related to the adverse events during follow-up after the CABG.

Therefore, the general agreement is that the SYNTAX score is of less significance in patients undergoing CABG, particularly since the randomized SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial did not associate any prognostic value of the SYNTAX score at 5 years [4]. The rationale is that for a coronary bypass it does not matter how complex the proximal lesions in the vessel are; these are always bypassed without any additional procedural complexity or surgical risk, provided there are suitable distal graft able targets. The SYNTAX score may be regarded as a marker of coronary anatomical disease complexity, and therefore is an indirect marker of plaque burden. Greater plaque burden, as evident by higher SYNTAX scores, may be one of the reasons why patients with higher SYNTAX scores derive more benefit from CABG, secondary to the graft 'protecting' the vessel, whereas a stent would treat the individual lesion. Nevertheless, the SYNTAX score will likely be related to outcomes in some degree; it is perceptible that a patient with a SYNTAX score of 80 will have an increased risk of adverse events as compared to a patient with a score of 20,6 since the SYNTAX score may be regarded as a marker for systemic atherosclerosis [5].

1.1.2. The Syntax Score in Practice

Based on data showing the usefulness of the SYNTAX score in PCI patients, the most recent European guidelines recommended that the SYNTAX score should be calculated for risk stratification in candidates for PCI (class of recommendation IIa, level of evidence B). Since the SYNTAX score lacks a prognostic value in patients undergoing CABG, the guidelines consider the SYNTAX score not to be effective/useful in candidates for CABG (class III, level of evidence B). This recommendation is, however, somewhat monochrome, since the SYNTAX score is useful for selecting PCI patients—a fact that allows the SYNTAX score to be useful for decision making between CABG and PCI. The SYNTAX score is helpful for identifying which patients would benefit most from either revascularization strategy, or thus in clinical practice it is useful to calculate in CABG patients as well [6]. In this regard, the American guidelines do take this into consideration and recommend calculation of the SYNTAX score in patients considered for both CABG and PCI equally, with a class/level of evidence of IIa/B. Guidelines are consistent in their optimal treatment recommendations for three-vessel disease as determined by the SYNTAX score. It is reasonable to perform PCI in patients with less complex 3 vessel disease (SYNTAX score ≤22), while CABG is clearly preferable in patients with more complex three-vessel disease (SYNTAX score >22). In patients with LM disease guidelines are more progressive.

In Europe indication to perform PCI in LM disease is a SYNTAX score ≤321 while the American guidelines use a SYNTAX score ≤22 as cut-off.3. However, a SYNTAX score cut-off ≤32 can be used if there is a low or intermediate risk of procedural PCI complications. The current treatment recommendations have been interpreted by many as a broadening indication to perform PCI. The introduction of the SYNTAX score has mainly reduced uncertainty in selecting which patients should undergo either CABG or PCI, although patient distribution to CABG and PCI has remained relatively stable [7]. Data from the SYNTAX run-in phase showed that 74% and 26% of patients with de novo three-vessel or LM disease underwent CABG and PCI, respectively. If the current revascularization guidelines are adhered to in clinical practice, 'new' distribution of patients recommended to undergo CABG and PCI might be considered to be approximately 75% and 25%, respectively. There remains an area of investigation regarding patients with LM disease and a SYNTAX score of 23–32 (approximately 6% of population). Ongoing EXCEL (Evaluation of Xience Prime versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial will provide necessary insights into safety and efficacy of PCI in this cohort. With a stronger recommendation to perform PCI in patients with LM disease and intermediate coronary complexity (SYNTAX score 23–32), 40% of total LM patient cohort can be referred to PCI. Using the SYNTAX trial & registries**Error! Reference source not found.**, estimated CABG/PCI distribution of patients with LM or three-vessel disease will then be 69% and 31%, respectively [8].

1.1.3. Limitations of the Syntax Score

SYNTAX score assessments have shown variability among investigators (inter-observer agreement) and even within different assessments of the same investigator (intra-observer agreement). This variability may be problematic because the optimal treatment recommendation could depend on the SYNTAX score. Introduction of observer bias may therefore result in inappropriate treatment decisions, especially when the SYNTAX score value is close to accredited cut-off values of 23 or 32. Non-invasive assessment of the SYNTAX score with CT and non-invasive functional assessment of lesions are being developed and will simplify the calculation of the SYNTAX score in the near future. To prevent inappropriate treatment recommendations, the SYNTAX score should not be a blind indication for treatment [9]. Although it is clear from the SYNTAX trial that patients with severe complex three-vessel disease (SYNTAX score ≥33) have superior outcomes with CABG.

Even patients with a SYNTAX score ≥33 may still undergo PCI if there are comorbidities that exclude the patient from undergoing CABG. In the SYNTAX PCI nested registry, 43% (82/189 patients) had a score ≥33.6 The SYNTAX score should therefore merely be one of the factors that is weighted by a multidisciplinary Heart Team consisting of a non-interventional/ clinical cardiologist, interventional cardiologist, and cardiovascular surgeon. The SYNTAX score is limited by the assessment of coronary disease complexity, while there are other clinical patient factors that are prognostically important and should be weighted by the Heart Team—for example, age, chronic obstructive pulmonary disease, and renal function. In an attempt to combine these factors, a number of new prediction models have been established. Initial validation of such models has been encouraging and further studies are forthcoming [10].

1.2. Noninvasive Imaging Modalities (e.g., Coronary Artery Calcium Scoring)

Over last 3 decades, CAC has emerged as a highly specific marker for coronary atherosclerosis. Agatston first described noncontract-enhanced, electrocardiographically gated computed tomography as an effective tool to quantify CAC in 1990 and improve cardiovascular risk assessment.

Since then, CAC has been studied extensively in myriad of population-based studies and has been shown to effectively stratify cardiovascular risk across ethnicities, irrespective of age, sex, and risk factor burden. Beyond risk stratification, CAC can identify high-risk patient subgroups who are more likely to benefit from more intensive primary prevention strategies. Quantification of CAC, distribution, location, and its association with high-risk plaque have added to our understanding of this innovative and yet simple decision tool [11]. The 2018 American College of Cardiology/ AHA/Multisociety cholesterol guideline recommends the selective use of CAC scoring in primary prevention to aid in decision-making process regarding statin therapy when there is uncertainty on the part of the clinician or patient. If the CAC score is >100 AU or 75th percentile of the CAC score distribution for a particular age/gender, initiating statin therapy is encouraged because of predicted strong net benefit. However, therapeutic inertia remains an issue in implementing novel preventive strategies in those with high CAC scores but without ASCVD events [12].

1.2.1. CAC Scoring for Cardiovascular Risk Assessment in Asymptomatic Patients

Beyond the issues related to scoring methodology and imaging technique, there remains the larger question of how the CAC score can be used clinically, particularly for cardiovascular risk assessment and guiding preventive therapies. Existing tools for achieving these end points include the Framingham risk score and the ASCVD risk, both of which are 10-year CHD risk metrics determined by using pooled cohort equations based on traditional risk factors such as age, sex, race, systolic blood pressure, serum cholesterol level, smoking history, and presence or absence of diabetes. Multiple studies have demonstrated that CAC measurements are also predictive of cardiovascular events [13]. It is important to note that the CAC level has been shown to have incremental value in the prediction of cardiovascular events. This means that there is no redundancy between the CAC score and any other traditional risk factor when it comes to predicting risk. Therefore, the addition of the CAC score to traditional algorithms & guidelines improves cardiovascular risk assessment & leads to better-informed clinical decision-making. One algorithm that includes CAC score developed by McClelland et al and is based on data from the Multi-Ethnic Study of Atherosclerosis (MESA). Based on collected patient data, including CAC score & any ascertained CHD events such as myocardial infarction, MESA risk score developed as a synthesis of both traditional risk factors and CAC score to estimate 10-year CHD risk [14].

1.2.2. Current Status of CT CAC Score in Clinical Guidelines

Although with the MESA risk score, CAC levels are used for risk assessment, this score is currently the only validated model to incorporate the CAC score. To date, several organizations have issued early recommendations regarding this matter, with the CAC score to be used situational as a supplement to shared decision making [15]. However, level of evidence backing these recommendations is moderate, and there remain several research gaps. For example, there is a lack of high-quality studies in which the effect that including the CAC score alongside traditional risk factors has on risk prediction and outcomes is directly evaluated, especially in underrepresented groups such as women and certain ethnic minorities. There is also a lack of high-quality studies on the cost effectiveness of using this approach. The CAC Consortium, a multicenter retrospective cohort study, recently established an association between CAC score and long-term cause-specific mortality. The Consortium suggested that the CAC score, in addition to being useful in predicting the risk of cardiovascular events, can also be used to identify high-risk subgroups, providing value beyond current guidelines in patients aged 30–49 years at high risk and patients with low risk and a family history of cardiovascular disease. The study also established that while patients with a CAC score higher than 1000 represent a distinct risk group, a CAC score of 0 can be a reliable negative risk factor for developing cardiovascular disease and for disease-specific mortality **Error! Reference source not found.**[16].

1.2.3. CAC Score as a Tool to Guide Statin Therapy

A primary benefit of using the CAC score is that it may help in reclassifying a patient's risk to a lower category such that statin treatment becomes unnecessary and is thus avoided. The 2013 American College of Cardiology/American Heart Association guideline on the treatment of blood cholesterol to reduce ASCVD risk in adults recommends statin treatment on the basis of low-density lipoprotein levels and other clinical cardiovascular risk factors. Subsequently, it was demonstrated that the addition of clinical risk factors leads to improvement in statin treatment eligibility. In a more recent model, the 10-year ASCVD risk is combined with the CAC score to guide primary prevention with statins. The current recommendation is to incorporate the CAC score as a decision-making tool to reclassify risk and guide statin therapy in patients older than 40 years who have borderline to intermediate (5%–20%) 10-year ASCVD risk. For patients with a risk of less than 5%, statin treatment is not recommended; as an exception, statin treatment may be recommended for select patients in this group with risk factors & a strong family history of coronary artery disease. For patients with a greater than 20% risk, statin treatment is recommended regardless of the CAC score **Error! Reference source not found.** [17].

1.2.4. CAC Progression and Follow-up Scanning

With the MESA risk score and modified decision-making model from Greenland et al, use of the CAC score is considered primarily in initial or baseline risk assessment. However, the low inter scan variability in CAC scoring makes the evaluation of CAC progression a relatively unexplored and debatable topic in the discussion. Score increases by about 20%–25% per year, and in about 20% of subjects with a CAC score of 0, the CAC score progresses to greater than 0 within 5 years and increases markedly with age but less so in women. It is also believed that CAC progression may reflect the efficacy of current medical management, prompting the question of whether more aggressive intervention is warranted [18]. While some studies have suggested that CAC progression, as compared with the baseline CAC score, may enable a more accurate prediction of cardiovascular events, others have argued that the baseline CAC score holds most of the prognostic value, with little to gain from repeat scans. These issues raise the essential question of what patient population is repeat CAC scanning

appropriate for in terms of prognostic value, radiation risks, and health care costs. It has been shown that patients with a CAC score of 0 both at baseline and 5 years later (the so-called "double zero") have the best prognosis. A double zero is associated with a very low 10-year risk (1.4%) and a new-onset CAC risk at 5 years of 1.8%. Therefore, repeat scanning in 5 years seems to be of benefit; of CAC [19].

Although an association between CAC progression and risk of cardiovascular events has been demonstrated, the supporting data are much less robust. Furthermore, it is unclear how CAC progression compares with baseline CAC score in terms of prognostic value. Nonetheless, it has been shown that CAC progression is linked to a higher risk of myocardial infarction and all-cause mortality. The CAC score increases by about 20%–25% per year, and in about 20% of subjects with a CAC score of 0, the CAC score progresses to greater than 0 within 5 years and increases markedly with age but less so in women. However, it may not benefit those who already had a double zero at CAC scanning or have already been classified as being at high risk because of a CAC score of 400 or higher. Relatively recent Society of Cardiovascular Computed Tomography guidelines recommend repeat CAC scoring at 5 years for patients with an initial CAC score of 0 and at 3–5 years for patients with a CAC score higher than 0, provided that the development or progression of CAC leads to an intensification or alteration in preventive management. In addition, one must be cautious in assessing the CAC scores in patients who are taking statins, as these scores might be falsely elevated despite the lower ASCVD risk, possibly owing to the calcification of previously soft plaques. For now, the usefulness of monitoring CAC progression demands further investigation and remains a work in progress [20].

1.2.5. CAC Score Acquisition Protocol, Calculation, and Interpretation

Modalities used for CAC scoring include electron-beam CT and multi detector CT, with latter associated with improved spatial resolution and largely replacing electron-beam CT in practice. Standard acquisition protocol involves axial multi detector CT performed with prospective electrocardiographic gating, a section thickness of 2.5 mm, and a section interval of 1 mm. The scan range is from below aortic arch to base of heart, and scanning parameters include a fixed tube voltage of 120 kVp and a variable tube current–time product, depending on patient's body mass index. Reconstruction parameters include a section thickness of 2.5 mm in both axial soft-tissue window and axial lung-window settings. The CAC score, specifically that calculated by using the Agatston method**Error! Reference source not found.**, is then obtained by using vendor-provided software, with calcification typically identified as high attenuation (130 HU) and an area greater than or equal to 1 mm^2 or larger. The Agatston score derived by integrating product of total plaque area and a cofactor based on attenuation of plaque calcium, in Hounsfield units.

CAC scores usually are reported for each of the coronary vessels and as a composite score for the entire image [21]. CAC scores can be interpreted in two ways: as absolute score with predetermined cutoffs or as a score adjusted for demographic parameters such as patient age and sex with use of several population databases such as the MESA database. Briefly, the MESA was a prospective multi-ethnic cohort study of the prevalence and progression of subclinical cardiovascular disease in 6814 patients from six U.S. communities. In the MESA, the age of participants was restricted to 45–64 years and patients with any cardiovascular comorbidities (ie, diabetes, hypertension, or hyperlipidemia) not included. Thus, the CAC score should be used primarily in asymptomatic individuals aged 45–64 years. Numerous studies have demonstrated efficacy of using the CAC scores to guide clinical management of patients with the coronary artery disease [21].

1.2.6. Prognostic Value of CAC in Symptomatic Patients

A large meta-analysis that evaluated 34,041 stable, symptomatic patients from 19 observational studies revealed a positive association between CACS and major adverse cardiac events. Mortensen et al. followed 23,759 symptomatic subjects for 4.3 years, and the incidence of CVD events increased with higher CACS. Another study of 3,691 symptomatic young subjects (18–45 years of age) with a median follow-up of 4.1 years showed that the highest event rate occurred in patients with more than 3 risk factors and CACS > 10 AU compared to CAC = 1–10 and CAC = 0 regardless of the number of risk factors. To sum up, CAC scanning in symptomatic subjects provides incremental prognostic information to guide the choice of diagnostic and therapeutic options [22].

2. Epidemiology of CAD Severity

2.1. Prevalence of Severe CAD in Different Populations

Asian ethnic groups present with a history of previous transient ischemic stroke, peripheral arterial disease (PAD), CABG, cerebrovascular accident, and ACS. In comparison to the White population, the Chinese had a more pronounced association between male gender and more severe CAD (OR 7.0 (4.0-12.6), p-value for interaction = 0.001). When comparing the triple vessel disease occurrence, the prevalence was highest in Malays (31.6%), then the Chinese (23.8%), followed by the Indians (23.2%). The severity of CAD was higher and independently associated with Chinese and Malay ethnicities compared to the White population. Consequently, other above-mentioned ethnicities exhibit greater CAD severity, so screening process for these races should be expedited. Around 11% of White patients had a STEMI when they arrived at the angiography lab, followed by Malay (8%), Chinese (7.6%), and Indian (7.5%) patients. Chinese people, Indian people, and Malay people had an increased rate for the unified category of NSTEMI or unstable angina (UA) than White people. So, White patients demonstrated higher levels of STEMI, whereas the other groups of patients presented with NSTEMI [23].

2.2. Impact of Risk Factors on CAD Severity

CAD is a prevalent and serious condition influenced by various risk factors, which significantly impact the severity of the disease, especially in patients with ACS. A large study based by Omidi et al based-on Tehran Heart Center's Data Registry investigated the relationship between conventional cardiovascular risk factors and the extent of coronary artery stenosis as measured. Among the study's 18,862 patients, age, sex, diabetes mellitus (DM), hypertension (HTN), dyslipidemia (DLP), family history, and myocardial infarction (MI) were identified as major

contributors to an increased Gensini score, indicating more severe coronary stenosis. Interestingly, while smoking and opium consumption were associated with higher positive Gensini scores, they did not significantly increase the severity of stenosis. The study emphasized that male gender and a history of MI were the strongest independent predictors of CAD severity, underscoring the need for targeted interventions in these populations. Additionally, DM was shown to play a significant role in worsening coronary stenosis, likely due to its contribution to atherosclerosis. Conversely, obesity presented an inverse relationship with CAD severity, a phenomenon referred to as the "obesity paradox." This finding, which suggests that obese individuals may have a lower risk of severe coronary stenosis, warrants further investigation to better understand its implications in clinical practice [24].

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