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MINI REVIEW ARTICLE

Coronary Artery Calcium Score, Could it Help Personalize Statin Use?

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ABSTRACT

Coronary Artery Calcium Score (CACS) a non-invasive imaging modality, which has aroused as a powerful tool to refine risk assessment and personalize statin therapy. The CAC score is used for guiding the use of statins in intermediate risk patients or borderline risk, in which statin use is uncertain. CAC scoring can reclassify risk in this group, guiding starting statin therapy.

There is a clear association between higher calcium density and lower risk of cardiovascular events using CT assessment of coronary artery calcium. This could be explained that when the proportion and density of calcium increases within the plaque, the plaque is stabilized and thereby reducing the risk of acute cardiovascular events and plaque rupture.

An important limitation is that no studies have evaluated the impact of preventive interventions guided by calcium score on hard event outcomes as well as CACS cannot exclude the presence of non-calcified atherosclerotic plaque, which often is more unstable and liable to rupture.

CACS can be a powerful tool for personalizing statin therapy in intermediate- and borderline-risk patients. CACS refines risk assessment, guides statin therapy and improves patient engagement.

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Introduction

Cardiovascular diseases (CVDs) are considered the leading cause of global morbidity and mortality [1]. Atherosclerosis is a chronic inflammatory process in which immune competent cells in lesions produce mainly pro-inflammatory cytokines. It is considered the major and primary contributor of cardiovascular diseases [2]. Statins, which decrease low-density lipoprotein cholesterol (LDL-C), have a pivotal role in preventing atherosclerotic cardiovascular disease (ASCVD) [3]. However, the decision to initiate statin therapy is often based on population-based risk calculators which may overestimate or underestimate the individual risk [4]. Coronary artery calcium (CAC) is a specific marker of coronary atherosclerotic burden that can be used to measure calcified subclinical atherosclerosis and is consequently important in cardiovascular risk stratification [5].

Coronary artery calcium scoring (CACS) could be used as a powerful tool for risk stratification. It is a non-invasive imaging modality that has emerged as a powerful tool to refine risk assessment and personalize statin therapy [6]. The Agatston scoring algorithm is used for quantifying CAC by using non-contrast computed tomography (CT). It is calculated as the product of total calcium area and a quantized peak calcium density weighting factor defined by the calcification attenuation in Hounsfield Units (HU). CACS represents a direct measure of subclinical atherosclerosis and was validated as a strong predictor of ASCVD events in different populations [7].

Evidence Based Studies

The 2018 American Heart Association (AHA)/American College of Cardiology (ACC) Guideline on the Management of Blood Cholesterol recommends the CACS to be used for guiding the use of statins in intermediate risk patients (5-20% 10-year ASCVD risk) or borderline risk (5-7.5% 10-year ASCVD risk, in which statin use is uncertain (8). In this stratum of intermediate-risk patients, the risk estimates may not accurately reflect their true ASCVD risk (9). CACS can reclassify risk in this group, guiding the initiation of statin therapy.

Multiple studies have shown that approximately 40-50% of intermediate-risk patients have a CACS of zero, indicating a low risk of ASCVD events. In these individuals, deferring statin therapy initiation may be reasonable, especially if other risk-enhancing factors are absent. On the contrary, a high CACS (≥100 Agatston units or ≥75th percentile for age, sex, and ethnicity) suggests a higher-than-anticipated risk, warranting statin therapy initiation [8].

In the Multi-Ethnic Study of Atherosclerosis (MESA), CACS was shown to significantly improve risk prediction. It demonstrated that CACS better predicts cardiovascular events in comparison to traditional risk factors. In MESA, participants with a CACS of zero had a 10-year ASCVD event rate of <3%, while those with a CACS >300 had an event rate of >20% (10). In borderline-risk patients, CACS was able to identify those who could benefit from early statin therapy. A CACS >0 in this group suggested the

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presence of subclinical atherosclerosis, supporting initiation of statin therapy. Conversely, a CACS of zero may reassure patients and clinicians that aggressive pharmacologic therapy with statins is not immediately necessary [11].

CAC Consortium (2022) is a large study of 66,636 asymptomatic adults which confirmed the MESA results. In this study, a CACS of 0 was associated with low 10-year cardiovascular mortality (0.2%), supporting statin deferral in this patient cohort (12). CACS is particularly useful in elderly, where traditional risk calculators may overestimate risk solely due to age. A CACS of zero in older adults is associated with a low risk of ASCVD events, potentially avoiding unnecessary statin use. On the other hand, a high CACS in this population may indicate a significant burden of atherosclerosis, supporting initiation of statin therapy [13].

Yet, there are multiple controversies and challenges regarding the CACS interpretation as well as the clinical impact of the presence of coronary calcification. CAC progression does not necessarily correlate with increased cardiovascular risk. In the PARADIGM registry, by serial CT scanning of over 2,000 lesions, calcified plaque volume was associated with higher cardiovascular events, while the percentage of calcified plaque volume (PCPV) was inversely proportional to cardiovascular events [14]. The major adverse cardiovascular events (MACE) as well as revascularization were lower in patients with higher in comparison to lower PCPV (MACE 9.4% versus 14.6%; p=0.022 and revascularization 8.8% versus 14.3%; p=0.016) [14].

These findings were consistent with the results of a sub-analysis of the MESA study which demonstrated the presence of clear association between higher calcium density and lower risk of cardiovascular events using CT assessment of coronary artery calcium [15]. This could be explained that when the proportion and density of calcium increases within the plaque, the plaque is stabilized and thereby reducing the risk of acute cardiovascular events and plaque rupture.

In a study published by Jin et al, although calcified plaque is a marker for risk of adverse events and disease progression, when considering the PCPV, increasing PCPV is a strong marker of plaque stability and reduced risk at both the lesion and patient level. A high CPV was associated with incident major adverse cardiac events (hazard ratio: 3.01: 95% confidence interval: 1.58 to 5.72), however high PCPV was inversely associated with major adverse cardiac events (hazard ratio: 0.529; 95% confidence interval: 0.229 to 0.968) in multivariable analysis[14].

Puri et al. explained that statin users exhibit higher CAC progression rate than non-users, which doesn't necessarily indicate worse cardiovascular outcomes. The results of this study revealed that independent of their plaque-regressive effects, statins promote coronary atheroma calcification. This reflects the shift from unstable to more stable plaques rather than disease progression [16].

In a meta-analysis of 10 studies published by Lee et al. in the European heart journal on statins and CAC progression, statin use was consistently associated with greater CAC progression. However, this progression was not linked to an increased risk of cardiovascular events supporting the theory that statins modify plaque composition rather than worsen disease [17].

The CACS has multiple limitations and risks. An important limitation is that no studies have evaluated the impact of preventive interventions guided by calcium scores on hard event outcomes. Another limitation of CACS is that it cannot exclude the presence of non-calcified atherosclerotic plaque, which often is more unstable and liable to rupture[18]. In addition, radiation exposure despite being minimal, and high cost may limit its use. Moreover, CACS is not recommended for low-risk individuals or those already at high risk, as it is unlikely to change management in these groups [19].

Recent research is exploring the integration of CACS with other biomarkers and imaging modalities, such as carotid intima-media thickness (CIMT) and high-sensitivity C-reactive protein (hs-CRP), aiming at refining risk assessment[20]. Artificial intelligence (AI) and machine learning algorithms may also enhance the predictive value of CACS by analyzing complex patterns in imaging data [21].

Conclusion

To sum up, CACS can be a powerful tool for personalizing statin therapy, especially in intermediate- and borderline-risk patients. By identifying subclinical atherosclerosis, CACS refines risk assessment, guides statin therapy initiation, and improves patient engagement. Although multiple limitations exist, ongoing research and technological advancements promise to further enhance its clinical utility. As personalized medicine continues to evolve, CACS will play an increasingly important role in optimizing cardiovascular risk management.

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