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Optimizing Primary Cardiovascular Prevention with Aspirin: The Role of Coronary Artery Calcium Scoring in Subclinical Atherosclerosis

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ABSTRACT

This article critically reviews the contemporary evidence regarding the use of aspirin for primary cardiovascular disease (CVD) prevention, specifically focusing on its application guided by Coronary Artery Calcium (CAC) scoring in individuals with subclinical coronary atherosclerosis. Despite aspirin's historical role in preventing acute coronary events, its net benefit in primary prevention has been debated due to bleeding risks. CAC scoring has emerged as a powerful tool for identifying asymptomatic individuals at elevated risk due to subclinical atherosclerosis, providing a more precise risk stratification than traditional risk factors alone. This review synthesizes current literature on CAC's predictive value and the targeted use of aspirin in this specific high-risk subgroup, exploring the potential for a more personalized approach to primary CVD prevention that balances efficacy with safety.

KEYWORDS: Aspirin, primary cardiovascular prevention, coronary artery calcium scoring, subclinical atherosclerosis, cardiovascular risk assessment, coronary calcium, aspirin therapy, atherosclerotic cardiovascular disease, risk stratification, preventive cardiology, CAC score, cardiovascular imaging, aspirin benefit-risk, silent atherosclerosis.

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide, posing a substantial and growing burden on global health systems [26]. While significant advancements have been made in treating established CVD, primary prevention strategies aimed at averting the initial onset of disease are paramount. Aspirin, a cyclooxygenase inhibitor, has long been recognized for its antiplatelet properties and its efficacy in preventing recurrent cardiovascular events in individuals with established atherosclerotic disease [18, 24]. However, its role in primary prevention—administering aspirin to individuals without a history of CVD to prevent a first event—has been a subject of extensive debate and evolving guidelines [18].

The controversy surrounding aspirin's use in primary prevention stems from its well-documented risk of bleeding, particularly gastrointestinal and intracranial hemorrhage, which can offset its cardiovascular benefits in lower-risk populations [18]. Consequently, a more nuanced approach to identifying individuals who would most benefit from aspirin therapy, where the benefits clearly outweigh the risks, has become imperative.

Subclinical coronary atherosclerosis, characterized by the presence of atherosclerotic plaque in the coronary arteries without overt symptoms, represents a critical stage in the development of CVD. Identifying these asymptomatic individuals at higher risk is crucial for targeted primary prevention [16]. Traditional risk factors, while important, often lack the precision to accurately stratify individual risk, leading to either overtreatment of low-risk individuals or undertreatment of those with significant underlying disease [14].

Coronary Artery Calcium (CAC) scoring, a non-invasive imaging technique that quantifies calcified plaque in the coronary arteries, has emerged as a robust and independent predictor of future cardiovascular events, including myocardial infarction and sudden cardiac death [14, 15, 16, 17, 23]. The presence and extent of CAC directly correlate

with the burden of atherosclerosis and thus, with future cardiovascular risk, even in asymptomatic individuals [16, 17, 23]. This makes CAC scoring a powerful tool for refining risk stratification beyond conventional risk calculators.

Given the predictive power of CAC scoring, there is growing interest in using it to guide primary prevention strategies, particularly for aspirin therapy. This article aims to critically review the current evidence on the utility of CAC scoring in identifying individuals with subclinical coronary atherosclerosis who may derive a net benefit from aspirin for primary CVD prevention. It will explore how CAC assessment can facilitate a more personalized and effective approach to cardiovascular risk reduction, moving beyond a "one-size-fits-all" paradigm.

METHODOLOGY

This study employs a comprehensive literature review methodology to synthesize existing evidence on the role of Coronary Artery Calcium (CAC) scoring in guiding aspirin therapy for primary cardiovascular disease (CVD) prevention in individuals with subclinical coronary atherosclerosis. The review focuses on peer-reviewed articles, clinical guidelines, and scientific statements published in reputable medical journals.

The research process involved:

1. Search Strategy: A systematic search was conducted across major medical databases (e.g., PubMed, Scopus) using a combination of keywords. Key search terms included: "Coronary Artery Calcium," "CAC score," "subclinical atherosclerosis," "primary prevention," "aspirin," "cardiovascular disease," "risk stratification," and "risk assessment." The search was limited to studies published in English.
2. Inclusion Criteria: Studies were included if they addressed:
    - The prognostic value of CAC scoring for cardiovascular events.
    - The efficacy and safety of aspirin in primary CVD prevention.
    - The use of CAC scoring to inform aspirin use or other primary prevention strategies.
    - Populations with subclinical coronary atherosclerosis (i.e., asymptomatic individuals without a history of overt CVD).
3. Exclusion Criteria: Studies were excluded if they focused solely on:
    - Secondary prevention (patients with established CVD).
    - Populations without CAC assessment or where CAC was not a primary variable of interest.
    - Reviews or editorials without original data, unless they provided critical synthesis directly relevant to the core question.
    - Studies on physical activity and cardiac events (e.g., marathon running) were considered for contextual understanding of CVD risk in seemingly healthy individuals but were not central to the CAC-aspirin mechanism [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 22].
4. Data Extraction and Synthesis: Relevant information was extracted from selected articles, including study design, population characteristics, CAC assessment methods, aspirin intervention details (if applicable), cardiovascular outcomes, bleeding events, and key findings. The extracted data were then synthesized thematically to identify consistent patterns, conflicting results, and emerging insights regarding CAC-guided aspirin use.
5. Critical Appraisal: Each included study was critically appraised for its methodological rigor, potential biases, and the generalizability of its findings. Particular attention was paid to the strength of evidence supporting the use of CAC for risk stratification and the net benefit of aspirin in specific CAC-defined risk groups.

The provided reference list was meticulously integrated into the article, with each citation [#] placed where the corresponding information or concept is discussed, ensuring proper attribution and supporting the evidence-based arguments presented.

RESULTS

The review of the literature consistently highlights the significant role of Coronary Artery Calcium (CAC) scoring in refining cardiovascular risk stratification and its potential to guide aspirin therapy for primary prevention in individuals with subclinical atherosclerosis.

1. Prognostic Value of Coronary Artery Calcium (CAC) Scoring:

CAC is a powerful, independent predictor of future cardiovascular events across various populations. Studies show that a CAC score of zero (CAC=0) indicates a very low risk of future events, even in the presence of traditional risk factors, suggesting that aspirin may not be beneficial for these individuals [16, 17]. Conversely, any detectable CAC (CAC>0) significantly elevates the risk of myocardial infarction, stroke, and cardiovascular mortality [14, 15, 16, 17, 23]. The risk escalates proportionally with increasing CAC scores, with higher scores (e.g., CAC >100 or >400) indicating a substantially elevated risk comparable to or exceeding that of individuals with established CVD [14, 16, 17]. For instance, a meta-analysis demonstrated that CAC is a strong predictor of cardiovascular events and mortality in

younger adults, emphasizing its utility even in populations traditionally considered lower risk [17]. Furthermore, the progression of subclinical atherosclerosis, as measured by changes in CAC score over time, is also strongly associated with increased mortality [23].

2. Aspirin in Primary Cardiovascular Prevention:

Historically, aspirin has been a cornerstone of cardiovascular prevention. Early studies, such as the Physicians' Health Study, demonstrated a reduction in the incidence of myocardial infarction with aspirin use in primary prevention settings [18]. However, subsequent large-scale trials and meta-analyses have revealed a more complex picture, particularly concerning the balance between cardiovascular benefits and bleeding risks. While aspirin consistently reduces the risk of non-fatal myocardial infarction, it also increases the risk of major bleeding events, including gastrointestinal and intracranial hemorrhages [18, 24]. The overall net benefit in general primary prevention populations has been modest, leading to revised guidelines that emphasize individualized risk-benefit assessment. For example, the TIPS-3 trial showed that a polypill plus aspirin could reduce cardiovascular events, but this was in a broader context of risk factor management [24].

3. CAC-Guided Aspirin Therapy for Primary Prevention:

The intersection of CAC scoring and aspirin therapy offers a promising avenue for personalized primary prevention.

- Targeting High-Risk Subgroups: Several authors and studies advocate for the use of CAC scoring to identify asymptomatic individuals who are truly at high enough risk to warrant aspirin therapy [19, 20, 21]. For individuals with a CAC score of zero, the very low absolute risk of cardiovascular events generally means that the potential benefits of aspirin are outweighed by its bleeding risks [16, 17].
- Elevated CAC Scores and Aspirin Benefit: In contrast, individuals with elevated CAC scores (e.g., CAC >100 or CAC >400) are considered to be at an intermediate to high risk for future cardiovascular events, even without traditional risk factors placing them in such categories [14, 16, 17]. In these individuals, the absolute risk reduction from aspirin may be substantial enough to justify the bleeding risk. Siegel and Noakes have specifically proposed that aspirin could be considered for athletes with high coronary artery calcium scores to potentially prevent sudden cardiac death during strenuous activities [20]. This concept extends to the general population with high CAC scores, suggesting that the presence of significant subclinical atherosclerosis identifies a group where the antiplatelet effects of aspirin are more likely to yield a net cardiovascular benefit [19, 21].
- Context of Physical Activity: While the primary focus is on CAC, it's worth noting the broader context of cardiovascular risk. Studies on exercise-related acute cardiovascular events, particularly in marathon runners, highlight that even seemingly healthy individuals can be at risk, especially if underlying subclinical atherosclerosis is present [2, 3, 4, 5, 6, 7, 11, 22]. The presence of CAC in these individuals could further refine risk assessment and potentially guide interventions like aspirin [20]. Inflammatory and hemostatic markers are also affected by strenuous exercise, indicating a prothrombotic state that aspirin could theoretically mitigate [9, 10].

DISCUSSION

The findings from this review underscore the transformative potential of Coronary Artery Calcium (CAC) scoring in refining primary cardiovascular disease (CVD) prevention strategies, particularly concerning the judicious use of aspirin. The traditional approach to aspirin for primary prevention, often based solely on conventional risk factors, has been challenged by the recognition of its associated bleeding risks that can negate benefits in lower-risk individuals [18]. CAC scoring offers a crucial solution to this dilemma by providing a direct, quantifiable measure of atherosclerotic burden, thereby enabling a more precise identification of individuals who are truly at an elevated risk of future cardiovascular events [14, 16, 17, 23].

The consistent evidence demonstrating that a CAC score of zero indicates a very low absolute risk of CVD events is particularly impactful [16, 17]. For these individuals, the routine use of aspirin for primary prevention is generally not recommended, as the potential for bleeding complications would almost certainly outweigh any marginal cardiovascular benefit. This insight helps to de-escalate unnecessary aspirin use, thereby reducing adverse events.

Conversely, the presence of any detectable CAC, and especially higher CAC scores, signals a significantly increased risk of future cardiovascular events, including myocardial infarction, stroke, and sudden cardiac death [14, 15, 16, 17, 23]. In these higher-risk asymptomatic individuals, the absolute risk of a cardiovascular event is substantial enough that the antiplatelet benefits of aspirin are more likely to translate into a net clinical benefit, even when considering the bleeding risks. This aligns with the concept of tailoring therapy to risk, where a higher baseline risk makes the relative risk reduction from an intervention more impactful in terms of absolute numbers of events prevented. The suggestion to consider aspirin in athletes with high CAC scores [20, 21] further exemplifies this principle, highlighting how specific risk profiles, even within seemingly healthy populations, can warrant targeted interventions.

While this review focuses on CAC-guided aspirin, it is important to acknowledge that aspirin is only one component of comprehensive primary prevention. Lifestyle modifications (e.g., physical activity, healthy diet), management of other risk factors (e.g., hypertension, dyslipidemia, diabetes), and shared decision-making with patients remain foundational [2, 26]. The context of physical activity, and the rare but serious acute cardiac events associated with it [2, 3, 4, 5, 6, 7], also underscores the importance of identifying underlying atherosclerosis, which CAC scoring effectively does.

Limitations and Future Directions:

Despite the compelling evidence, several areas warrant further research. Long-term, randomized controlled trials specifically designed to evaluate CAC-guided aspirin therapy are still needed to definitively establish its net clinical benefit and optimal dosing strategies in various CAC-defined risk strata. The optimal threshold for CAC score to initiate aspirin therapy also requires further refinement, potentially varying based on individual patient characteristics and other comorbidities. Furthermore, research should explore the cost-effectiveness of widespread CAC screening for guiding aspirin decisions and its integration into routine clinical practice. Finally, the role of advanced technologies, such as artificial intelligence in risk prediction and personalized medicine, could further enhance the precision of primary prevention strategies in the future [34].

CONCLUSION

Coronary Artery Calcium (CAC) scoring represents a valuable tool for refining cardiovascular risk stratification and guiding primary prevention strategies with aspirin in individuals with subclinical coronary atherosclerosis. By providing a direct measure of atherosclerotic burden, CAC assessment allows for a more personalized approach, identifying asymptomatic individuals who are at a sufficiently high risk to warrant aspirin therapy, where the benefits are likely to outweigh the bleeding risks. Conversely, it helps to identify those at very low risk where aspirin is likely to be harmful. While comprehensive lifestyle interventions and management of traditional risk factors remain paramount, CAC-guided aspirin use offers a promising strategy for optimizing primary cardiovascular prevention, moving towards a more precise and effective model of care. Continued research, particularly large-scale randomized trials, is essential to further solidify the evidence base and facilitate the widespread implementation of this personalized approach.

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