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Coronaries, Calcium, and Kidney Consequences

Brian Rifkin[1] and Anthony Valeri[2]

[1]Division of Nephrology, Hattiesburg Clinic, Hattiesburg, Mississippi, USA; and [2]Department of Nephrology, Columbia University Irving Medical Center, New York, New York USA

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Cardiovascular disease encompasses various conditions, including myocardial infarction, stroke, heart failure, arrhythmia, and valvular heart disease. Atherosclerotic cardiovascular disease (ASCVD) is specifically defined by accumulation of plaque in the coronary arteries, leading to luminal narrowing. Abrupt rupture of coronary plaques may lead to thrombosis with subsequent heart attack and death. ASCVD is the leading cause of morbidity and mortality worldwide. Therefore, identifying asymptomatic people at risk is pivotal for physicians to guide decision-making for primary prevention. The coronary artery calcium score (CACS) is a hallmark of coronary artery atherosclerosis. A computed tomography scan for coronary artery calcium (CAC) examination is a cheap, fast, low radiation exposure test accomplished without contrast injection. It provides prognostic information over other traditional cardiovascular risk markers and established scoring systems; and may indicate the need for pharmacologic interventions (Figure 1).[1]

Vascular calcifications are not simply the result of aging. Ectopic bone production, a common feature of atherosclerosis, is the basis for CAC influenced by inflammatory, metabolic, and transcriptional factors. Inflammation, propagated by apolipoproteins and oxidized phospholipids in the artery wall, is instrumental for both development of atherosclerosis and vascular calcification. Chronic kidney disease (CKD) and end-stage kidney disease are often defined by elevated systemic inflammatory states. Unfortunately, patients with CKD face additional risks for tissue calcification due to associated mineral and bone disorders, (i.e., elevated FGF-23, hyperphosphatemia, 1, 25-vitamin D deficiency, and secondary hyperparathyroidism) which may lead to calcification of the intima, and perhaps more importantly, the media of coronary vessels.[2,3] Metabolic factors play a significant role in the excessive regional distribution of arterial wall calcium in patients with kidney disease.

Numerous lifestyle modifications have been shown to influence ASCVD risk including diet, exercise, smoking, and physical activity. For decades it has been known that medications that lower cholesterol are also beneficial to at-risk patients. The impact of coronary plaque formation can be estimated from the total cumulative exposure of an individual to low-density lipoprotein cholesterol, and lowering lipid levels is important for reducing the risk of both primary and secondary ASCVD events. Therefore, HMG-CoA reductase inhibitors (also known as statins), for the reduction of serum low-density lipoprotein cholesterol, are a cornerstone of treatment for patients with ASCVD. In addition, statin eligibility in lower-risk patients may be best determined by measuring CACS.

Cardiovascular disease burden is known to be several-fold higher in patients with CKD. Unfortunately, patients with CKD do not appear to get the same degree of mortality benefit from statin therapy as those without CKD.[4,5] In addition, the benefits of statins appear to wane in patients with more advanced stages of CKD. The SHARP trial, one of the only CKD-specific lipid-lowering trials, showed an overall statistically significant 17% reduction in major cardiovascular events, but a nonstatistically significant reduction in mortality.[6] Most patients in the SHARP trial were with CKD 4 or 5, and approximately 3 times more participants progressed to end-stage kidney disease than had a major cardiovascular event during the study. Although Kidney Disease: Improving Global Outcomes guidelines currently recommend statins for patients with CKD not on dialysis, little is known about how statins affect CACS in patients with CKD.

Correspondence: Brian Rifkin, Division of Nephrology, Hattiesburg Clinic, 415 South 28th Ave, Hattiesburg, Mississippi 39402, USA. E-mail: brian.rifkin@hattiesburgclinic.com; or Anthony Valeri, Columbia University, 622 West 168th Street, Rm PH4-124, New York, New York 10032, USA.amv3@cumc.columbia.edu

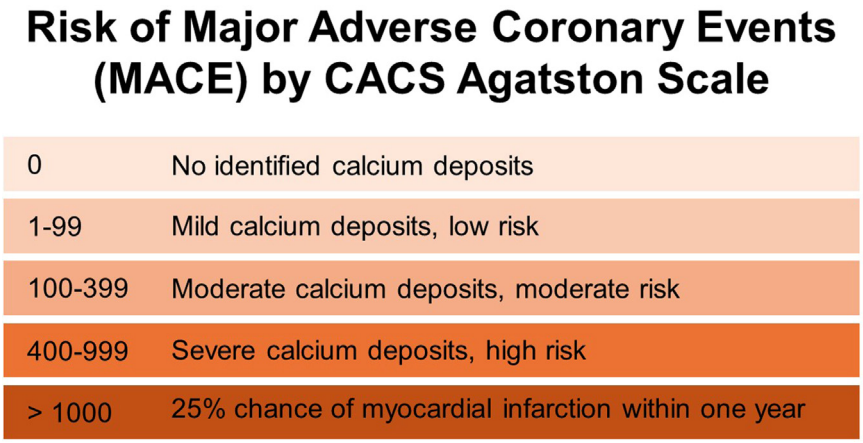

Figure 1. Risk of major adverse coronary events (MACE) by CACS Agatston scale. CACS, coronary artery calcium score.

In this issue of KI Reports, researchers report on an analysis of patients in a large observational prospective trial from Korea (the KNOW-CKD study).[7] In a previous paper, the authors of KNOW-CKD reported that high CACS were associated with an increased risk of rapid CKD progression, similar to findings in SHARP.[8] The current analysis was performed on 1137 patients, with statin utilization defined as >50% use during the follow-up period. After 4 years, 52% of participants showed CACS progression. The multivariate-adjusted odds ratio for CACS progression in statin users, compared to statin nonusers, was 1.78 (95% confidence interval: 1.26–2.50). This association was preserved after adjustment of various cardiovascular risk factors. Antithetically, the authors found a greater progression of CACS in patients with CKD treated with statin therapy. This phenomenon had been previously noted in patients without CKD and may not be clinically significant according to the US Preventive Services Task Force.[9]

Despite the adverse effect of statin therapy on progression of CACS, statins have beneficial effects that may help reduce the risk of cardiovascular events. Vascular plaque stabilization by means of plaque volume reduction, as well as decreasing inflammation and thrombosis are just a few benefits of statins. In fact, incorporation of calcium into plaques has been shown to be beneficial for stabilization of atheromas.[S1] In the end, it is acute events, including myocardial infarction, progression to end-stage kidney disease and death that are most clinically relevant. Are progressive CACS in patients with CKD just "incidentalomas" (radiologic findings without clinical significance)? The real-world implications of statin-related CACS

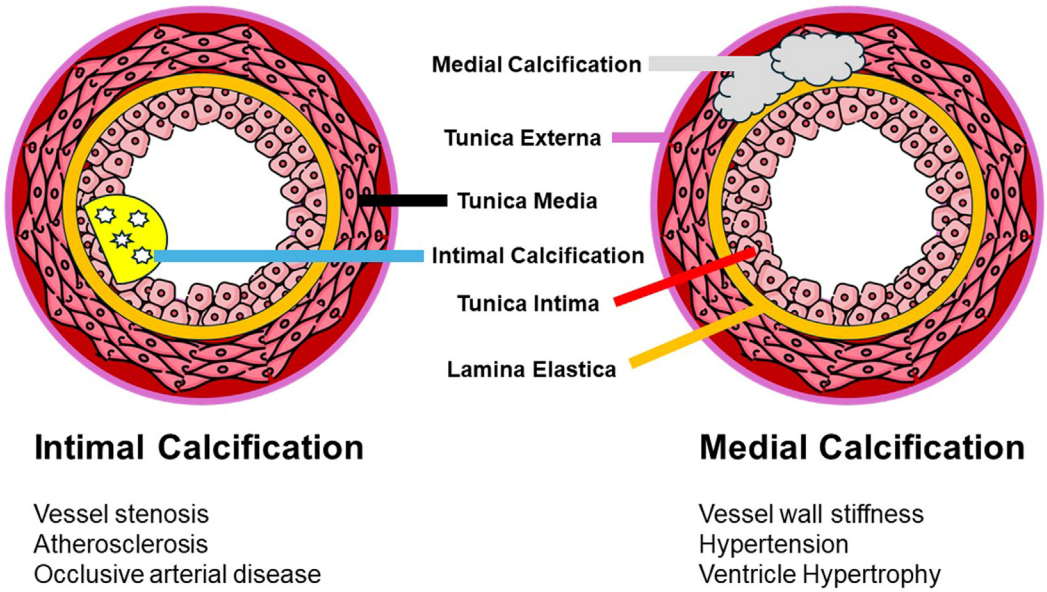

Figure 2. Consequences of intimal versus medial calcifications on vascular disease.

progression were not specifically addressed but would be interesting for future investigation. Finally, this study did not imply any adverse effects of statin use despite the progression of CACS.

As the authors report, this is the only large, well-organized study that demonstrated an association between statin use and CACS progression in predialysis patients with CKD. It is important to note, not all CAC is created equal. Although CAC volume is directly correlated with CVD risk, CAC density at a certain CAC volume is inversely associated with CVD risk.[S2] Statin-induced CACS progression might be related to intimal calcification rather than medial calcification. Intimal calcification is characterized by macrophage accumulation, and as stated above, may be beneficial to plaque stabilization. In contrast, medial calcification leads to upregulation of osteogenic regulatory genes, creating a cycle of further mineralization, decreasing vessel compliance and increasing systolic pressure and ventricular afterload[S3] (Figure 2). It is hypothesized that cardiovascular protection by statin is weaker in advanced CKD due to metabolic deregulation of calcium and phosphorus, leading to prolific medial calcium accumulation and greater non-ASCVD cardiac disease.[S4]

This study was limited by its observational design, an inability to control for confounders, and thus it cannot prove the existence of causality between statin use and CACS progression. In addition, the authors did not measure calcium density and regional distribution (intima vs. media), or atheroma total volume, which may be significant factors when attempting to correlate CACS to ASCVD events and outcomes. Next, many of the patients in this study had early CKD (66.3% with G1–G3a) and only 25% had diabetes, thus the results may not be generalizable. Overall, this was not a "high risk" cohort for cardiovascular events. The authors conceded that ASCVD events were relatively low, again making no correlation between progressive CACS and coronary events. Finally, due to limited follow-up (8 times over 4 years), the authors admit they may have missed patients taking statins intermittently, and thus misclassified patient use. Future studies should have more frequent data collection to understand the exact percentage of time patients are using statin medications; and examine barriers to directed use. Additional research could focus on the calcium volume, location and density, and its correlation with ASCVD events in high-risk patients with CKD.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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