The "power of zero" CAC validated for absence of ischemia on PET?

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In this issue of JNC, Van den Hoogen et al provide further evidence for the "power of zero," a term for the high negative predictive value (NPV) of a coronary artery calcium (CAC) score of zero for the absence of obstructive coronary artery disease (CAD) and low cardiovascular risk in both asymptomatic and symptomatic patients. They extend the value of zero CAC to the prediction of absent ischemia on PET myocardial perfusion imaging (MPI) in symptomatic patients. Further studies in diverse populations with higher cardiometabolic and inflammatory risk factor burden, including the prognostic value of CAC to predict nonobstructive plaque and coronary microvascular dysfunction, would be important future extensions to this novel work.

CAC scoring has been most utilized in asymptomatic patients at intermediate risk for purposes of risk stratification and guidance of preventive therapies, which is reflected in the joint 2019 American College of Cardiology and American Heart Association Primary Prevention guidelines.[1] Recently, there has been an increased interest in the use of CAC in symptomatic patients to avoid further testing and provide cost-effective care in low-to-intermediate risk patients. In an era of declining obstructive CAD, traditional pre-test likelihood models such as the Diamond-Forrester model significantly overestimate probability for obstructive CAD,[2] and CAC can effectively reclassify many patients to low likelihood.[3] This was further shown in a recent meta-analysis of studies of CAC of zero[4] finding a NPV of 97% for obstructive CAD on CCTA and low major adverse cardiac event rate of 0.5-0.8% per year. The 2021 multi-society Guideline for the Evaluation and Diagnosis of Chest Pain includes a class IIa recommendation for CAC risk stratification in low-risk patients with stable chest pain and no known CAD.[5] However, much of the available evidence supporting the high NPV of CAC of zero is based on studies using CCTA to diagnose obstructive CAD,[4] which is sensitive but not as specific for anatomic obstructive CAD with associated ischemia compared to nuclear MPI.[6]

In the current study by Van den Hoogen et al, 647 symptomatic chest pain patients were sequentially referred to coronary CT angiography (CCTA) with CAC score, followed by PET MPI if there was suspected anatomic obstructive CAD (defined as $> 50\%$ stenosis on CCTA). The authors found a high NPV of 97.8% for CAC of zero for anatomic obstructive CAD-induced ischemia on $[^{15}O]H_2O$ PET as defined by stress myocardial blood flow (MBF) of < 2.4 mL·min^{-1}·g^{-1}. A CAC of zero constituted about a third of referred patients. Adding CAC to a multivariable model increased the discriminatory ability for obstructive CAD with ischemia compared to risk factors and symptoms. However, the PPV for CAC > 0 was only 34.6%, highlighting that if any coronary artery calcification is present, the risk for obstructive CAD is uncertain and not necessarily low, and additional testing may be required.

The current study with a sequential study design provides valuable and novel evidence of the value of a

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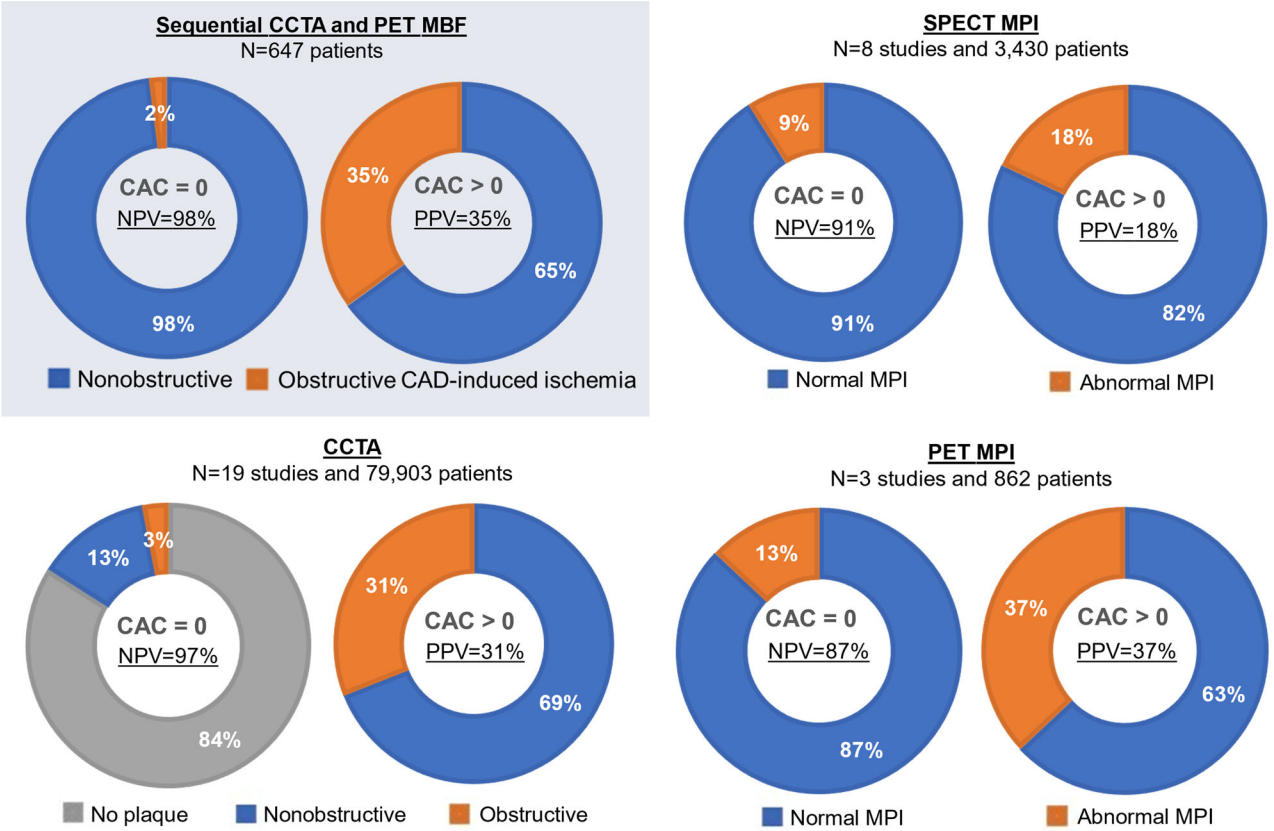
CAC of zero to rule out ischemia on PET MPI due to obstructive CAD in a population of symptomatic chest pain patients. It complements prior studies demonstrating the predictive value of a CAC of zero for obstructive CAD on CCTA and nuclear MPI (Figure 1). It is one of the few prospective studies to assess the value of sequential use of testing for chest pain. The recently presented PRECISE CT trial[7] showed that the sequential use of a clinical risk score (PROMISE Minimal Risk Score) followed by CCTA with or without functional testing with CT fractional flow reserve in elevated-risk patients led to an 82% lower rate of catheterization without increase in other cardiovascular events compared with a usual testing approach in patients referred with chest pain. The integration of CAC into the sequential testing approach may further improve risk stratification and further reduce need for downstream testing.

Prior studies of the prognostic utility of a CAC of zero for the absence of inducible ischemia on MPI have had mixed results. A meta-analysis of the predictive value of CAC for ischemia on PET and SPECT MPI[8] found a lower overall pooled NPV of 93.4%, with a wide range from 74.9 to 100%. For instance, a 2008 study of 695 patients found a much lower NPV of 84% for ischemia in patients with CAC of zero.[9] Overall cardiovascular event rate was low when CAC was zero (0.8% per year) but was even lower in patients with a CAC of zero AND without ischemia (0.3% per year) suggesting additive value of assessment for ischemia for risk prediction. The patients in the current study compared to this prior study had a lower prevalence of diabetes (14 vs 29%), lower BMI (28.1 vs 32.4 $kg \cdot m^{-2}$), and higher prevalence of smoking (35 vs 14.2%) and were from Finland with a different racial and ethnic makeup and therefore may have had a lower prevalence



Adapted from Agha AM et al JACC Cardiovasc Imaging 2022 and Bavishi C et al. JACC Cardiovasc Imaging 2016
Abnormal MPI: abnormal summed stress score; Obstructive CCTA: ≥ 50% stenosis; Obstructive CAD-induced ischemia: ≥ 50% stenosis on CCTA and PET stress MBF < 2.4 ml/min/g

Figure 1. Multimodality validation of the ''power of zero'': predictive value of CAC for findings of obstructive CAD on sequential CCTA and PET (Van den Hoogen et al.) compared to meta-analyses of other imaging modalities.

of noncalcified obstructive stenosis. Additionally, the design is important as the sequential testing approach of the current study excluded patients with nonobstructive CAD on CCTA from undergoing PET MPI and does not capture patients with ischemia due to nonobstructive CAD (INOCA) or coronary microvascular dysfunction (CMD).

So how do we apply the ''power of zero''? The value of a CAC of zero to avoid further diagnostic testing may depend on the underlying risk of the population for noncalcified plaque which may be higher in cardiometabolic, renal, and systemic inflammatory diseases (SIDs). It will miss patients with coronary microvascular dysfunction or nonobstructive plaque with associated ischemia thereby missing the opportunity to effectively treat symptoms and institute risk modification therapies. It is well established that patients with coronary microvascular dysfunction defined as myocardial flow reserve (MFR) < 2 are a higher risk population. In a recent study of mostly symptomatic patients referred for Rubidium-82 PET MPI who had a CAC of zero, 10% had abnormal perfusion results, and 17% had abnormal MFR < 2.[10] There is increasing evidence that coronary vascular dysfunction may precede or coexist with high-risk nonobstructive atherosclerosis, in the absence of coronary calcification, particularly in certain populations such as systemic inflammatory disorders.[11,12] In addition, noncalcified plaque is associated with increased risk, and 13% of patients with a CAC of zero had nonobstructive noncalcified plaque on CCTA in a meta-analysis of stable chest pain patients.[4] Although patients with a CAC of zero in this meta-analysis had low short-term risk (defined as $< 1\%$ annual cardiovascular event rate over $<$ 3-year average follow-up in stable chest pain), those patients with noncalcified plaque may be at higher risk over longer-term follow-up. While it could be argued that repeat CAC testing might identify patients who have clinically significant progression in plaque, one can also argue that earlier treatment of such disease may be of value.

In summary, this is an important study and provides further evidence that a CAC of zero may have value in symptomatic patients to avoid unnecessary testing and potentially improve cost effectiveness of care, particularly when the diagnostic question is ''does my patient have obstructive CAD with associated ischemia?''. It does not obviate the need for clinical judgment in potentially higher risk patients with higher likelihood of noncalcified plaque, ischemia without obstructive CAD, and coronary microvascular dysfunction. Further studies of the value of CAC of zero in symptomatic patients are needed in diverse populations with higher cardiometabolic and inflammatory risk factor burden, including the assessment of myocardial blood flow in all patients not just those with anatomic obstructive CAD. Additionally, an approach for the use of CAC of zero in symptomatic patients as part of a sequential testing algorithm will require future studies to determine the influence on longer-term cardiovascular outcomes, and to determine the ''warranty period'' before further testing should again be considered.

Disclosures

The authors have reported that they have no conflict of interest relationships relevant to the contents of this paper to disclose. The author financial disclosures include: Dr. Weber reports personal consulting fees from Horizon Therapeutics and Kinisika, outside of the submitted work.

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