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Guidance for Sponsors
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Coronary Artery Calcium Scoring in Clinical Trials

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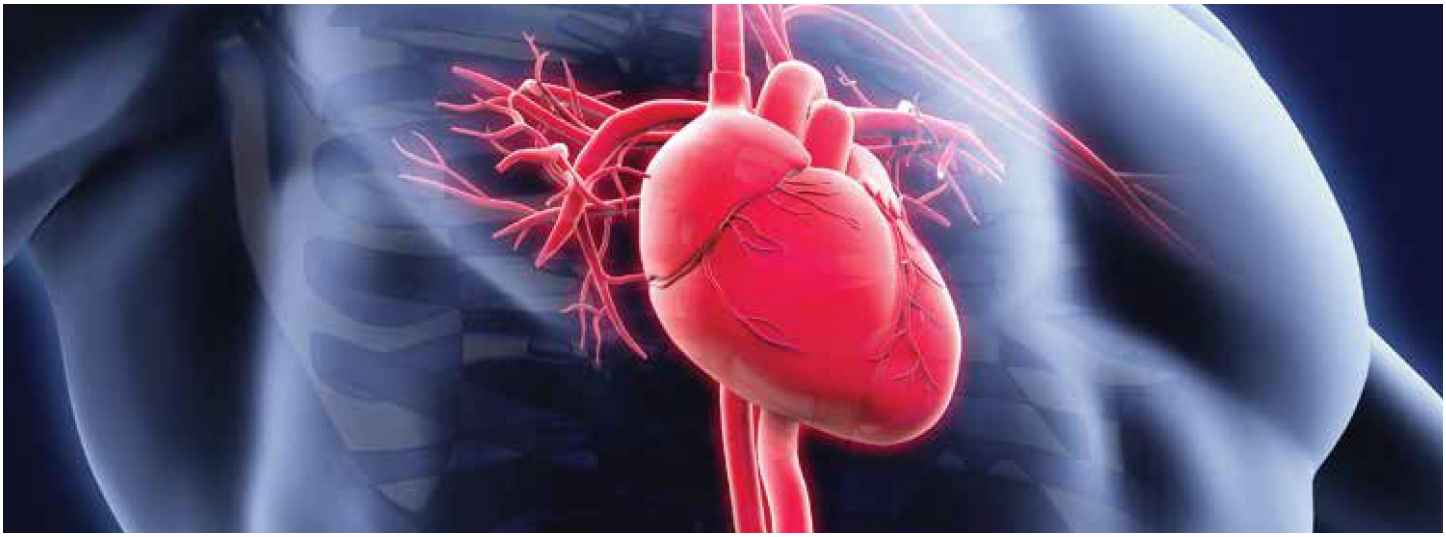

Coronary artery calcium scoring is one of the most powerful and economical predictors of cardiovascular risk, and an established biomarker in trials of preventive therapy. Yet the score is less simple than it appears. Calcium density carries prognostic information of its own, scores vary between scanners, vendors and software, and photon-counting CT is now changing the measurement itself. This issue reviews the method, the CAC-DRS reporting system and the sources of variability that sponsors must control when calcium scoring supports a trial endpoint.

Introduction

Cardiovascular disease caused 915,973 deaths in the United States in the most recent reporting year, and the majority of these deaths are related to coronary heart disease. Its direct and indirect costs reached an estimated $414.7 billion in 2021–2022.[1] Biopharmaceutical companies are investing heavily in new therapies, and among the biomarkers available to monitor them, coronary artery calcium (CAC) scoring is one of the best established.

The Agatston Score

Atherosclerosis progresses from lipoprotein retention in the arterial wall to cholesterol deposition, inflammation and, ultimately, calcification. The Agatston score, developed on electron-beam CT and now measured on multidetector CT, quantifies that calcium. Each lesion's area in square millimeters is multiplied by a weighting factor determined by its peak attenuation in Hounsfield units, and the products are summed across the coronary tree.

Because coronary calcium correlates strongly with atherosclerotic plaque burden, the score is a robust predictor of cardiac events. Scores are traditionally stratified as minimal (1–10), mild (11–99), moderate (100–399) and severe (400 and above), and scores above 400 signal markedly increased risk. The Coronary Artery Calcium Data and Reporting System (CAC-DRS), published in 2018, standardized reporting by combining the score category with the number of involved vessels and linking each category to treatment recommendations.[2]

The Density Paradox

The Multi-Ethnic Study of Atherosclerosis (MESA) complicated this picture. Among more than 3,000 participants with detectable calcium, greater calcium volume predicted more coronary and cardiovascular events, but at any given volume, higher calcium density was associated with fewer events.[3] Dense, stable calcification appears to be relatively protective. Because the Agatston score rewards density, it may overstate risk in some patients, and the MESA investigators concluded that area or volume scores alone are not optimal measures of risk.[3] This matters for trials of therapies, such as statins, that may increase calcium density while stabilizing plaque.

Sources of Variability

Calcium scoring remains the mainstay of assessment, and its value in a trial depends on the quality and consistency of the data. Three alternative measures exist: the Agatston score, the volume score and calcium mass. Mass, calibrated against a phantom, is the most physically meaningful and the least dependent on acquisition. A multi-institutional, multimanufacturer international standard defined how calcium mass should be quantified to allow consistent measurement across platforms.[4]

Scanner and software differences are substantial. In a study of state-of-the-art scanners from four vendors, calcium scores differed significantly, enough to reclassify up to 6.5% of patients into a different risk category.[5] Different software packages applied to the same images can also produce different results.[6] For trials that compare scores over time, or pool data across sites, these differences can rival the treatment effect being measured.

Photon-Counting CT

Photon-counting detector CT, first cleared by FDA in 2021, counts individual X-ray photons and measures their energy.[7] It offers higher spatial resolution, less noise and lower radiation dose, and can reconstruct images at selected energy levels. It also changes calcium scores: in phantom studies, routine photon-counting protocols produced higher Agatston scores than conventional CT, and agreement depended on the reconstruction energy and settings used.[8] Photon-counting CT promises more precise plaque characterization, but sponsors cannot assume that its scores are interchangeable with those from conventional scanners.

Guidance for Sponsors

Calcium scoring in a trial

- **Lock the scanner and protocol.** Scan each subject on the same scanner, with the same tube voltage, slice thickness and reconstruction, at every visit.[5]
- **Specify the analysis software.** Use a single validated software version throughout the trial.[6]
- **Calibrate.** Use phantom calibration and consider reporting calcium mass and volume alongside the Agatston score.[4]
- **Capture density.** Record volume and density to support exploratory analysis of plaque stabilization.[3]
- **Plan for photon-counting CT.** Prespecify how scans from photon-counting and conventional systems will be handled.[8]
- **Read centrally.** Use blinded core laboratory analysis with documented quality control.[9]

Summary

Coronary artery calcium scoring is an inexpensive, widely available and powerful predictor of cardiovascular risk. Its use as a trial biomarker requires an appreciation of what the score measures, how calcium density modifies risk and how scanners, software and the arrival of photon-counting CT alter the numbers. With standardized acquisition and central analysis, calcium scoring remains a precise and dependable tool for evaluating new cardiovascular therapies.

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About Intrinsic Imaging, LLC

Intrinsic Imaging is an ISO certified medical imaging CRO and imaging core lab providing comprehensive services in support of Phase I-IV clinical trials and Class I, II, III medical device trials. Intrinsic Imaging is also a world leader in conducting Artificial Intelligence studies. With its team of more than 650 board-certified and fellowship-trained physicians, Intrinsic Imaging's team has sub-specialization in all therapeutic areas, including Cardiovascular, Central Nervous System,Gastroenterology, Musculoskeletal, Oncology and Ophthalmology. Certified by the British Standards Institution (BSI), Intrinsic Imaging is the only company in the world to hold five ISO certifications specifically for providing imaging core lab services on clinical trials. For more information, please visit www.IntrinsicImaging.com.

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