GUEST EDITOR'S PAGE

Cardiovascular Imaging in Clinical Trial Design

A Vision for Sustainability

Suvasini Lakshmanan, MD, MS,[a] Alessia Gimelli, MD[b]

We have witnessed dramatic advancements in cardiovascular (CV) imaging over the last few decades with the expansion of the clinical utility of noninvasive multimodality imaging, technological advances in image acquisitions, artificial intelligence (AI)/machine learning–based innovations, and research in molecular imaging.[1,2] These developments provide a unique platform for personalized CV medicine based on early phenotyping of cardiac disease, accurate risk stratification, prognostication, guidance for management, and monitoring the response to therapy. In parallel, we have also seen tremendous growth in the size of, complexity of, and necessity for CV clinical trials to inform evidence-based care for our patients.[3] This exponential development of trials has been associated with significant challenges in costs, efficiency, and the likely cascading effects of inequity and the underrepresentation of appropriate participants in large-scale trials.[4] Today, we stand at a crossroads as we try to envision the future of CV care while navigating the paradoxes of precision medicine and value-based health care, equity, financial toxicity, and technological innovations vs global sustainability. The integration of CV imaging techniques and biomarkers in clinical trials, particularly in various stages of trial design, can provide an innovative strategy to enrich trials and accelerate progress toward sustainable and personalized care.[5,6] CV imaging can improve our mechanistic understanding of the underlying pathophysiology of disease at the molecular level, and these insights can elucidate the role of potential novel therapies. In this review, we seek to provide insights on the role of CV imaging in the enrichment of clinical trial design by using techniques that can ensure precise risk stratification for efficient patient recruitment and targeted management, paving the way for robust and personalized outcomes.

PATIENT SELECTION AND RISK ENHANCEMENT BY PHENOTYPING

Cardiac phenotyping by imaging has paved the way for early and accurate risk stratification, prognostication, and the ability to offer targeted therapies. Trial enrichment by CV imaging thereby leverages phenotyping by imaging biomarkers and the identification of specific patient subgroups based on grades of risk, disease severity, or molecular characteristics on imaging data. By focusing on well-defined patient cohorts, trials can optimize the chances of understanding the mechanistic basis of disease and detecting meaningful treatment effects, thereby paving the way for smaller and financially efficacious trials.

Subclinical atherosclerosis identified by coronary artery calcium (CAC) on contrast chest/cardiac computed tomography (CT) as well as coronary plaque burden and characterization by cardiac CT angiography (CCTA) have been identified as independent prognostic imaging biomarkers with the ability to provide enhanced risk stratification and potentially guide targeted treatment for primary and secondary CV prevention.[7,8] A National Heart, Lung, and Blood Institute workshop has eloquently described the potential role of CAC/atherosclerosis-based risk stratification and AI-enabled opportunistic CAC screening

From the [a]University of Iowa Hospitals and Clinics, Iowa City, Iowa, USA; and the [b]Fondazione Toscana G. Monasterio, Pisa, Italy.
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in pre-existing CT scans in primary prevention trials.[9] The ROBINSCA (Risk or Benefit in Screening for Cardiovascular Disease) trial demonstrated that CAC scoring identified fewer participants to be at increased CV risk (relative reduction for women: 37.2%; for men: 28.8%); therefore, less preventative treatment was indicated in this group compared to the group that used traditional risk scores.[10] Contemporary trials, including CorCal (Effectiveness of a Proactive Cardiovascular Primary Prevention Strategy, With or Without the Use of Coronary Calcium Screening, in Preventing Future Major Adverse Cardiac Events), CAUGHT-CAD (Coronary Artery Calcium Score: Use to Guide Management of Hereditary Coronary Artery Disease [CAD]), and SCOT HEART 2 (Computed Tomography Coronary Angiography for the Prevention of Myocardial Infarction), will compare the impact of imaging-guided management (CAC for CorCal and CAUGHT-CAD and CCTA for SCOT-HEART 2) on clinical outcomes vs the standard of care.[11] These trials will indicate if the relatively smaller sample size in design, as calculated by imaging-based risk stratification, is sufficient to identify differences in outcomes. The landmark ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) used a CCTA-guided strategy in the initial step of the study design to rule out left main coronary disease and nonobstructive disease and thereby identify participants with moderate to severe ischemia who could be randomized to an invasive vs a conservative strategy. The early use of the CCTA-based strategy in the trial has provided us with trial enrichment in terms of identifying the most appropriate patients for randomization. Subsequent AI-based plaque characterization has demonstrated the incremental prognostic ability of anatomic assessment over ischemic evaluation of disease.[12] Phenotyping can help us evaluate the risk-benefit profile of proposed interventions along a spectrum of CV risk, especially in participants with extremely low risk of CV events. An interim analysis of a sample cohort of the WARRIOR (Women's Ischemia Trial to Reduce Events in Nonobstructive CAD) with suspected ischemia with no obstructed coronary arteries randomized by CCTA or invasive coronary angiography showed a differential baseline CV risk of participants by modalities.[13] The majority of participants in that study had normal coronaries with no evidence of plaque, suggesting that noninvasive workup with CCTA may be favorable to reduce any incremental adverse events and costs typically associated with invasive coronary angiography.

Cardiac magnetic resonance (CMR) allows for excellent tissue characterization of the myocardium and can detect expansion of extracellular volume using T_1 mapping, which reflects diffuse interstitial fibrosis, and focal midwall fibrosis using late gadolinium enhancement, which are known to have prognostic implications. Myocardial fibrosis in aortic stenosis (AS) has clinical implications, with ventricular decompensation and irreversible scarring, and hence serves as a potential biomarker in clinical trials to serially monitor myocardial characterization, which can optimize the timing of aortic valve replacement and allow for the development of medical therapies.[14,15] To this effect, the ongoing EVOLVED (Early Valve Replacement Guided by Biomarkers of Left Ventricular Decompensation in Asymptomatic Patients With Severe Aortic Stenosis) trial is the first multicenter randomized trial that will seek to evaluate if asymptomatic patients with severe AS and midwall late gadolinium enhancement identified by CMR will benefit from early aortic valve replacement, with reduction in long-term morbidity and mortality, compared with routine care.[16]

Applications of transthoracic and transesophageal echocardiography, including measurements of cardiac structures, remodeling/function, and valvular hemodynamics, have been incorporated in numerous cardiac trials, most recently for evaluating cardiotoxicity in oncology and interventional device therapies.[17] Advances in AI promise to identify new biomarkers in echocardiography that can enable early phenotyping of a variety of pathologies and thereby enhance risk stratification to be incorporated in large-scale trials.

OPTIMIZING THE CONDUCT OF CLINICAL TRIALS WITH IMAGING

AI can play a crucial role in the implementation of primary prevention trials by leveraging the opportunistic screening of imaging biomarkers from pre-existing scans that can inform further management. NOTIFY-1 (Incidental Coronary Calcification Quality Improvement Project) leveraged a validated deep learning algorithm to enable opportunistic CAC screening from prior nongated lung CT scans and demonstrated that notification of incidental CAC can increase statin prescription rates.[18] Future trials must evaluate the effect of AI-enabled opportunistic screening in CV imaging on clinical outcomes and, particularly, the cost-effectiveness of trials.

TRIAL CONCEPTS: MECHANISTIC TRIALS AND SURROGATE ENDPOINTS IN CV IMAGING

Noninvasive modalities can provide novel insights into the pathophysiology and progression of heart disease that can provide a mechanistic understanding of the natural history of disease, which can assist in risk stratification and the clinical development of novel therapies. A mechanistic trial provides useful information about the efficacy of therapies in a small trial powered for the progression of surrogate imaging/molecular targets, which can guide efficient and cost-effective planning of phase 3 trials.

Serial CCTA trials allow for monitoring the progression of coronary atherosclerotic plaque burden and characteristics; physiologic assessment by CT fractional flow reserve; and novel markers that serve as modifiers of CV risk, such as pericoronary fat attenuation index and epicardial fat volumes.[8,19] Measures of coronary plaque burden, especially low-attenuation plaque, have been identified as independent markers of adverse events and serve as markers of interest as surrogates to clinical endpoints in serial imaging trials.[20] Therapeutic trials with serial imaging inform the mechanisms of action of novel therapies, and integration with genetics and -omics will continue our efforts toward precision CV medicine. In the EVAPORATE (Effect of Vascepa on Improving Coronary Atherosclerosis in People With High Triglycerides Taking Statin Therapy) trial, icosapent ethyl (IPE) was associated with significant regression of low-attenuation plaque volumes on serial CT compared with placebo over 18 months, thereby providing key mechanistic insights on the action of IPE that could explain the CV outcome benefit beyond the lowering of triglycerides. Subsequent post hoc analysis of EVAPORATE have shown additional benefits of IPE on prognostically relevant imaging parameters, including coronary physiology and plaque morphology.[21] These changes in surrogate endpoints correlated with the timeline of reduction in clinical events of CV mortality and the need for revascularization in REDUCE-IT (Reduction of Cardiovascular Events with EPA–Intervention Trial).[22] Against the background of developments of novel antiatherosclerotic therapies, serial CCTA trials can be done on a smaller scale with less financial burden and can provide crucial data on the feasibility of a treatment and its effects, which can influence trial design and the high costs incurred with larger long-term trials. In the field of valvular disease, prospective studies that used serial CT identified valvular calcification and subclinical fibrosis in AS as markers of disease progression and predictors of adverse CV outcomes.[15] CT calcium scoring is now incorporated in major guidelines for risk stratification and can assist in guiding contemporary treatments, including the clinical development of medical therapies.[23] The development of novel molecular imaging radiotracers and radiopharmaceuticals that target inflammatory leucocytes, fibroblasts, and neurohormonal signaling cascades can enable early detection of CAD.[24]

[18]F-fluorodeoxyglucose positron emission tomography enables the visualization of plaque vulnerability and inflammation and has been used to understand the therapeutic effectiveness and anti-inflammatory properties of statins.[25] Hybrid positron emission tomography imaging with CMR/CT enables specific imaging of fibrosis activity and the early detection of fibrogenesis before end-stage scar formation, thereby allowing us to understand disease progression in myocardial remodeling, and can provide insights into interventions for earlier and optimal treatment of at-risk patients. Radiolabeled fibroblast activation protein–specific inhibitor tracers have demonstrated favorable imaging properties at reasonable radiation levels and are being actively studied in prospective clinical trials to understand myocardial fibrosis activity in myocardial infarction and cardiomyopathies.[26,27] These studies are expected to provide data on disease tracking that correlate with clinical status and inform the development of antifibrotic therapies.

CONCLUSIONS

There is an urgent need for a paradigm shift in CV clinical trials to focus on sustainability as well as equity in enrollment and representation of participants. As we embrace the opportunities afforded by CV imaging in the enrichment of clinical trial design, the trials of the future will hopefully ensure a more nuanced understanding of the pathophysiology of heart disease and patient phenotypes as well as the continued development of novel and personalized therapies in an efficient and cost-effective manner.

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ADDRESS FOR CORRESPONDENCE: Dr Alessia Gimelli, Imaging Department, Fondazione Toscana Gabriele Monasterio, Via Moruzzi, 1, Pisa, Italy. E-mail: gimelli@ftgm.it.

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