Outcomes Research in Cardiovascular Imaging: Report of a Workshop Sponsored by the National Heart, Lung, and Blood Institute

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In July of 2008, the National Heart, Lung, and Blood Institute convened experts in noninvasive cardiovascular imaging, outcomes research, statistics, and clinical trials to develop recommendations for future randomized controlled trials of the use of imaging in: 1) screening the asymptomatic patient for coronary artery disease; 2) assessment of patients with stable angina; 3) identification of acute coronary syndromes in the emergency room; and 4) assessment of heart failure patients with chronic coronary artery disease with reduced left ventricular ejection fraction. This study highlights several possible trial designs for each clinical situation. (J Am Soc Echocardiogr 2009;22:766-773.)

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Cardiovascular imaging is a source of innovation and controversy for the health care community. Cardiologists and radiologists are now capable of obtaining high quality images that describe myocardial function and perfusion, define risk of major clinical events, and show coronary anatomy without need for invasive instrumentation.[1] At the same time, there is concern that the rapid dissemination of cardiovascular imaging is a prime example of a costly technology that is enthusiastically embraced without appropriate supporting scientific evidence.[2,3]

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Dr. Greenland served as a consultant to GE and Toshiba, and received a small honorarium from Pfizer for a role on a Visiting Professor Selection Committee. Dr. Peacock is on the Scientific Advisory Board, or is a consultant or speaker for Abbott, Beckman Coulter, Biosite, Heartscape, Inovise, Inverness, Ortho Clinical Diagnostics, and The Medicine's Company. He has received research grants from Abbott, BAS, Biosite, Brahms, Heartscape, Inovise, Inverness, EKR, and the Medicine's Company. Also, he has an ownership interest in Vital Sensors. Dr. Udelson is co-PI of the ROMICAT-2 trial, sponsored by the American College of Radiology Imaging Network (ACRIN). He has received research funding and has served as a consultant to Lantheus Medical Imaging and Molecular Insight Pharmaceuticals. Drs. Douglas and Taylor are co-first authors. Reviewers for this article are: Stephan Achenbach, MD, Associate Editor, *JACC: Cardiovascular Imaging;* Thomas Marwick, MBBS, PhD, Associate Editor, *JACC: Cardiovascular Imaging;* Christopher Kramer, MD, Associate Editor, *JACC: Cardiovascular Imaging;* Vasken Dilsizian, MD, Associate Editor, *JACC: Cardiovascular Imaging.*

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During the past 5 years, medical imaging has grown substantially, with Medicare Part B costs alone increasing from $6.89 billion in 2000 to $14.11 billion in 2005 (105%) of which an estimated one-third is cardiovascular.[3,4] In addition, there is inconsistent use, with some areas of the country having utilization rates 10 times those of others.[5] There is no clear explanation for the rapid growth; it cannot be ascribed entirely to aging of the population, changing disease rates, or improved outcomes.[3,4] The "value" of imaging in terms of improved health outcomes or reduced cardiovascular events remains subjective, with limited evidence, often generated with flawed research methodology.[6,7] There are also concerns that imaging can cause harm,[8,9] that there are few rigorous regulatory controls, and that utilization is at least in part driven by self-referral[10] and, in some cases, even direct-to-consumer advertising.[11]

A commonly cited model for efficacy in imaging describes 6 hierarchical tiers of evidence: 1) technical efficacy; 2) diagnostic accuracy; 3) diagnostic thinking; 4) therapeutic efficacy; 5) patient outcome; and 6) societal efficacy.[12–14] A recently convened American College of Cardiology–Duke University think tank on imaging quality in cardiovascular medicine,[15] noted that imaging research has primarily focused on diagnostic and prognostic accuracy, with little work directed at determining the direct impact of imaging on patient outcomes. As a result, among 745 recommendations for cardiovascular imaging in American College of Cardiology and American Heart Association guidelines, only 1% are based on Level of Evidence: A.[16] In contrast, in cancer medicine, randomized trials have been completed or are under way for assessing the ability of imaging technologies to prevent major clinical events due to breast[17] or lung cancer.[18]

TRIAL DESIGN CONSIDERATIONS

Methodology

Though it may seem logical that diagnosing disease with "better" imaging tests will yield better outcomes, there are reasons why this may not be so. For example, some disease detected by sensitive technologies in fact reflects subclinical disease that if left alone would never become clinically manifest.[19] This was discovered during large-scale

studies of mass screening for neuroblastoma in children.[20] Another unintended consequence of advanced imaging may be the detection of "nontarget" findings, such as noncalcified lung nodules, that may not have clinical relevance but require additional testing and/or procedures. Therefore, a number of scientists have argued that a preferred way to definitively determine whether or not any new diagnostic test improves outcomes is through properly designed randomized trials using clinical events as outcomes.[21] However, there are a number of major methodological difficulties in designing and implementing randomized trials in which imaging tests themselves are the target of randomization.[6] Effects, by definition, have to be indirect as tests do not directly affect clinical status. Instead we must presume that they lead clinicians and patients to modify behavior, which hopefully will lead to fewer clinical events.

Several issues represent important considerations when planning trials to determine if imaging can affect outcomes.

Comparison group

The initial consideration is whether one is testing a strategy of performing an imaging test versus not performing any imaging, or whether a comparison is desired between distinct imaging modalities. As an example of the latter design, 103 patients with chronic coronary artery disease (CAD) and left ventricular (LV) dysfunction being considered for revascularization[22] were randomized to either single-photon emission computed tomography (SPECT), myocardial perfusion imaging (MPI) or positron emission tomography (PET) for determination of viability. The imaging information was provided to clinicians for decision making blinded with regard to the imaging modality (with polar maps showing areas of ischemia, infarction, and the like) and patients were followed for 2- to 3-year outcomes. There was no difference in event-free survival between the 2 groups, suggesting that the use of either imaging modality to inform revascularization decisions results in similar outcomes. An ongoing study that represents the "imaging versus no imaging" approach is the WOMEN (What is the Optimal Method for Ischemia Evaluation in WomeN?) study, in which women with suspected CAD are randomized to an initial evaluation strategy of SPECT MPI versus an initial exercise electrocardiography (ECG) testing strategy, with the end point of 2-year negative predictive value for outcome events.[23] These studies demonstrate that it is feasible to subject imaging modalities to the same rigorous comparisons that are standard for therapeutics.

End points

An area of substantial uncertainty in the evaluation of imaging outcomes is the appropriate end points for use in trials. Ideally, end points would involve important natural history outcomes such as death, cardiac death or composites of cardiac death, and nonfatal cardiovascular events including myocardial infarction (MI). However, the many decisions made "downstream" from the imaging results have a highly significant effect on outcomes, such that the imaging results themselves are only 1 of many influences on outcomes, and thus challenging to isolate. This has led to considerations of other end points occurring over a shorter time horizon, including such metrics as cost-to-diagnosis, cost-to-predict event, cost-to-prevent nonfatal events, and behavior change with risk factor modification.

Efficacy versus effectiveness

Efficacy refers to the performance characteristics of a test under ideal conditions performed and interpreted by experts. *Effectiveness* refers to test performance under "real-life" conditions.[24] An efficacious test does not necessarily translate into an effective test, and ideally imaging modalities would be subject to both types of analysis. Stowers et al.[25] reported SPECT imaging efficacy in a small study of 46 emergency department (ED) patients randomized to resting SPECT perfusion imaging or conventional clinical strategy. Length of stay and costs were lower in the imaging strategy arm. Effectiveness of rest perfusion imaging was studied in the ERASE Chest Pain (Emergency Room Assessment of Sestamibi for the Evaluation of Chest Pain) trial, in which over 2,500 patients were randomized to an initial ED evaluation strategy of resting SPECT perfusion imaging, in addition to standard testing, or to a nonimaging standard evaluation strategy.[26] The results demonstrated a reduction in unnecessary hospital admissions associated with the imaging strategy, suggesting significant effectiveness of imaging in this situation.

THE NHLBI WORKSHOP ON IMAGING OUTCOMES RESEARCH

The National Heart, Lung, and Blood Institute (NHLBI) recently released its strategic plan for "Shaping the Future of Research".[27] The importance of optimizing diagnostic tests for improving outcomes is explicitly recognized in the plan, which states that "research is needed to evaluate the extent to which risk stratification and application of personalized approaches can improve effectiveness" (Challenge 3.1.a); that "studies are needed to reduce the inappropriate used of diagnostic tests and treatments" (Challenge 3.1.c); and that there is a need to "evaluate the risks, benefits, and costs of diagnostic tests and treatments in representative populations and settings" (Challenge 3.2.a).

Therefore, on July 21 and July 22, 2008, the NHLBI convened experts in noninvasive cardiovascular imaging, outcomes research, statistics, and clinical trials to develop a vision for imaging research that transcends current reliance on diagnostic and prognostic end points to a new paradigm that focuses on preventive and therapeutic value, where value implies an improved clinical outcome and/or reduced costs. The panel was specifically charged to develop a set of recommendations for future analyses and possible research funding by NHLBI, including sample trial designs for 4 pre-defined clinical scenarios commonly encountered in clinical practice. The 4 scenarios were: 1) screening the asymptomatic patient for CAD; 2) assessment of stable angina; 3) identification of acute coronary syndromes in the emergency room; and 4) assessment of heart failure patients with chronic CAD with reduced LV ejection fraction. The panel was asked to identify need, assess feasibility, and determine 1 to 2 examples of possible trial concepts for each scenario. Given the time limitations, it was recognized that these trial overviews would subsequently require substantial statistical and logistical analysis to become formal, detailed, and actionable trial designs.

SCREENING THE ASYMPTOMATIC PATIENT FOR CAD

Forty years ago, the World Health Organization[28] first published principles around which screening programs can be justified Table 1, and many of these principles also apply to vascular diseases such as CAD. Screening for abdominal aortic aneurysm is now an accepted practice for some patient groups based on multiple randomized controlled trials.[29–31] However, there are also a number of unknowns that have