Journal of the American College of Cardiology Vol. 50, No. 20, 2007

Published by Elsevier Inc.

ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.09.007

EDITORIAL COMMENT

Not All Randomized Trials Are Equal*

K. Lance Gould, MD, FACC

Houston, Texas

The study by Beanlands et al. (1) in this issue of the *Journal* is a multicenter, randomized trial in 430 patients with coronary artery disease (CAD) and left ventricular ejection fraction ≤35% to determine whether a management strategy that included F-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging to guide revascularization improved clinical outcomes compared with standard care where FDG PET was not available. On the basis of strict statistical analysis, the results show that PET FDG imaging for guiding revascularization did not improve outcomes compared with standard management without FDG PET.

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This study adheres to every detail of a randomized trial except for one weakness—25% of the patients with PET-indicated revascularization did not have it done. From one point of view, the authors are correct in concluding that the primary end point, results of PET FDG imaging, had no benefit compared with standard management for this group of patients. However, to the extent that 25% of patients with PET-indicated revascularization did not have it done, the study is substantially a trial of whether the deciding physician chose to adhere to treatment indicated by PET FDG on the basis of "clinical judgment" and/or bias against revascularization.

The adherence failures or crossovers reduce the difference between control and treated groups that might then become statistically insignificant for the number of subjects in the study. In post hoc analysis of the "adherence to PET subgroup" of this report, the hazard ratio was 0.62 with $p = 0.019$ for 38% fewer events than the control group, a maximal difference that is not sufficient to offset the negative bias of adherence failures in the entire treated group. Therefore, adherence failures in the subjects assigned to the PET group might cause a negative bias against treatment that might otherwise be proven effective with a larger study.

In the report by Beanlands et al. (1), failure of randomized management might be due to bias against revascularization in Canada, failure to quantify viability sufficiently to convince a clinician, or extended clinical circumstances not considered in enrollment criteria. Whatever the reason, it de-powers the study to a negative or inconclusive outcome for the initially estimated size. Thus, the experimental design failed to anticipate adherence failures with increased number of subjects needed to power the study adequately.

In contrast, extensive published data demonstrate that, for patients with large enough areas of viable ischemic myocardium to reduce ejection fraction, any of several measures of viability might serve as an adequate indicator for revascularization, including single-photon emission computed tomography (SPECT) imaging, stress echocardiogram, magnetic resonance imaging, post-systolic potentiation, and so forth, so that PET imaging is not unique for this purpose (2). Although negative or inconclusive as a management trial, this report illustrates a basic problem of complex clinical management trials in which treatment success or definitive conclusions might depend on physician or patient bias and/or on asking the right question for the specific unique strengths of the imaging technology.

In contrast to this article from Canada, in the U.S., a large number of revascularization procedures are done in stable CAD, owing to the opposite bias by physicians doing these procedures despite extensive randomized trials demonstrating no reduction in death or infarction, as in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive DruG Evaluation) trial (3), the most recent of many reports with the same conclusions. The DEFER (Deferral of PTCA Versus Performance of PTCA) trial (4) further showed that physiologic assessment of stenosis severity is a valid guide for reducing unnecessary revascularization procedures with optimal outcomes. The off-label use of drug-eluting stents is associated with significantly higher risk of death or myocardial infarction than on-label use (5), but off-label use remains widespread.

An interesting survey of invasive cardiologists (6) confirms the impression that most stenosis seen at coronary arteriography will likely be stented regardless of data from randomized trials to the contrary and concludes, "Although cardiologists might believe they are benefiting their stable patients with CAD by performing PCI [percutaneous coronary intervention], this belief appears to be based on emotional and psychological factors rather than on evidence of clinical benefit." Another quote from the article is also germane: "The only thing that would really change is if there had been an imaging study—and it would have changed it not by how you responded to the catheterization, but by not doing the cath at all" (6).

*Editorials published in the *Journal of American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From The Weatherhead P.E.T. Center for Preventing and Reversing Atherosclerosis, University of Texas Medical School at Houston, Department of Medicine, and the Memorial Hermann Hospital, Houston, Texas.

JACC Vol. 50, No. 20, 2007
November 13, 2007:2013–15

And what imaging study should be performed before the coronary arteriogram—stress electrocardiogram, SPECT, or echocardiogram tests? All undoubtedly prevent to some extent unnecessary diagnostic arteriograms and associated stents. However, all are also commonly falsely positive, leading to unnecessary arteriograms and procedures, or are falsely negative, which undermines their use for reducing diagnostic catheterizations. Despite its explosive popularity, the computed tomography (CT) angiogram with a resolution limit of 0.625 mm cannot differentiate between a 23% and 77% diameter stenosis of a 3-mm coronary artery as compared with quantitative arteriography in principle and in published fact. It thereby serves to prevent some caths by ruling out any CAD in some patients but might lead to more unnecessary caths by failing to differentiate severe from non-severe stenosis in more patients, because atherosclerosis is so common. It therefore shares with the other imaging technologies the mixed effects that reinforce the dominance of invasive procedures without scientific basis. The lack of reliable precision in all of these imaging technologies reinforces a fundamental interventional bias that complicates any imaging-management study of CAD.

And thus we return to cardiac PET—what are its unique strengths? And what is the right question for a trial related to these issues? Cardiac PET is unique for 2 strengths. The first is reliably quantifying relative radionuclide uptake (relative myocardial coronary reserve) without attenuation artifacts for small, relative 5% to 10% regional perfusion differences in precise arterial distributions, even for tertiary small branches (7–16). The second is quantifying absolute myocardial perfusion and absolute coronary flow reserve that are unique for assessing diffuse disease, multiple stenosis, mixed diffuse-stenotic or left main disease.

This quantitative capacity provides definitive stand-alone information for identifying early CAD or quantifying severity of more advanced stenotic or diffuse CAD where small changes in arterial diameter that cannot be quantified on an arteriogram have magnified effects on perfusion images, because flow is related to the radius raised to the fourth power. Our current routine determination of absolute coronary flow and flow reserve in all patients has been an eye-opener for deciding on invasive procedures, particularly for identifying severity of stenosis in the best relative perfused areas of the heart or for identifying the specific artery causing angina in complex multi-stenosis disease.

Although cardiac PET is in principle and in careful practice the best way of assessing coronary artery disease as a guide to management and invasive procedures (7–16), cardiac PET can easily be really messed up (17). Cardiac PET-CT is particularly subject to mis-registration artifacts with standard commercial software that fails to address this problem (17). This reviewer was the first to define the fluid dynamics of coronary artery stenosis in vivo, to relate stenosis severity to perfusion imaging, and to report pharmacologic stress imaging from planar to PET technology. Even with training in physics, physiology, and medicine, and a focused lifelong passion (motivation!) for the task, assessing coronary blood flow and myocardial perfusion imaging, reliably as a clinical guide for my management of CAD with minimal invasive procedures and maximal outcomes has become satisfactory to me only within the past few years.

The requirements for the "ultimate imaging test" for CAD were understanding the physiology, developing the technology or correcting faulty inadequate technology, and proving it to myself in clinical practice—and it works as the optimal guide to invasive procedures by eliminating unnecessary catheterizations, lowering overall costs, following the effects of intense medical treatment, and optimizing outcomes (7–16). If it did not, this reviewer would shelve PET and use whatever other technology was inherently better.

Thus, the "bias" of this reviewer is obvious. However, that bias is built on confirmed observations over the past 35 years and on a near-obsessive criticism of imaging technologies compared with physiologic insights needed, particularly for cardiac PET, which leaves a very small coterie of friendly or receptive colleagues sympathetic to this viewpoint. Therefore the lesson should be clear. The "ultimate imaging" in CAD to balance the powerful invasive bias of cardiology is PET, a complex imaging technology that is absolutely definitive in managing CAD and requires specialized, experienced, and critical clinical practitioners. It also requires randomized trials asking the right questions and powered to account for everybody's imaging biases, including the invasive bias of cardiology with crossovers among randomized groups.

The balance between invasive and noninvasive management of stable CAD is changing on the basis of outcomes of randomized intervention trials. Cardiac PET, done properly, potentially offers a definitive quantitative guide to disease severity, for following its changes, and as the reliable gatekeeper to invasive procedures on the basis of substantial scientific published data, but needs better-designed randomized trials.

Reprint requests and correspondence: Dr. K. Lance Gould, The Weatherhead P.E.T. Center, University of Texas Medical School, 6431 Fannin Street, Room 4.256MSB, Houston, Texas 77030. E-mail: K.Lance.Gould@uth.tmc.edu.

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