

Is Appropriate Use Criteria for Cardiac Radionuclide Imaging in Asymptomatic Diabetic Patients Evidence Based?

We write in reference to the recent article in the *Journal*, the 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging (RNI), which was published by the American College of Cardiology and endorsed by many other professional societies (1). This document was anticipated to impact physician decision making, test performance, and reimbursement policy.

We find the use of RNI for asymptomatic patients with diabetes mellitus (patients >40 years old) and other coronary risk equivalents that were considered appropriate in that document without sufficient evidence. Diabetic patients have a high incidence of coronary artery disease (CAD); therefore, an intensive primary and secondary prevention is recommended by various professional societies. But the strategy of routine RNI for all asymptomatic patients cannot be considered appropriate. The DIAD (Detection of Ischemia in Asymptomatic Diabetics) study was a prospective randomized trial evaluating outcomes after screening for asymptomatic CAD in type 2 diabetic patients (2). Although the study was underpowered to detect the pre-specified difference, due to a low rate of cardiac events, it ruled out any major benefit of routine screening. Even moderate or large defects had a positive predictive value of just 12% for cardiac events. Also, there was no apparent difference in the use of interventions for risk modifications between the 2 groups based upon results of screening. The recent BARI 2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes) trial, which randomly assigned patients with type 2 diabetes and stable CAD to immediate revascularization with intensive medical therapy versus only intensive medical therapy, failed to show to any difference in mortality or major cardiovascular events (3). The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial also showed that percutaneous intervention with optimal medical therapy was no better than optimal medical therapy alone for patients with stable CAD in general and for a subgroup of patients with diabetes specifically (4).

Thus, so far, revascularization has not proven beneficial for patients with asymptomatic or stable patients with CAD in terms of mortality and major cardiac events. A possible benefit of relief from angina does not hold true for subjects who are asymptomatic at baseline. In all of these trials, large proportions of patients in both groups received aggressive evidence-based interventions for cardiovascular risk reduction as recommended by various professional societies, and that could explain the low event rates. So, if an aggressive risk reduction strategy for asymptomatic high-risk patients can lead to a substantial decrease in cardiac events without any additional benefit from revascularization, the role of additional cardiac RNI is unclear. Routine RNI can be of use, if we can identify a subgroup of asymptomatic patients with additional risk factors who can benefit from revascularization or screening. The American Diabetic Association acknowledges the dearth of evidence in support of screening asymptomatic diabetic patients for CAD, and deemed it controversial (5).

The Centers for Disease Control estimates that about 33.9% of the U.S. population older than 40 years of age have diabetes (6). As per the appropriate use criteria, these patients would represent a high-risk group for whom cardiac RNI would be considered appropriate. In most places, a cardiac RNI would cost about U.S. \$700 to \$1,400. That would put enormous pressure on health care resources without any clear benefit.

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doi:10.1016/j.jacc.2009.08.048

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Reply

We greatly appreciate the comments of Dr. Sethi and colleagues regarding the use of radionuclide imaging (RNI) in an asymptomatic but high-risk patient, such as one with diabetes mellitus, which constitutes one of the indications noted in the recently published RNI appropriate use criteria (AUC) (1). Their letter correctly describes the low event rate noted in the DIAD (Detection of Ischemia in Asymptomatic Diabetics) study (2). Furthermore, information from the BARI-2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes) study (3), as well as that from the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) study (4), fails to support the benefit of revascularization, at least with regard to major cardiovascular events. At the present time, diabetic patients are still considered by clinical practice guidelines to be a high-risk/coronary artery disease-equivalent cohort, although that may change in the future. However, neither the BARI-2D study nor the DIAD study data were available at the time of the rating for the radionuclide AUC. Additionally, both of these

trials had a highly selected population of diabetic patients, which may not be representative of the risk for cardiovascular events in the general diabetic population.

Perhaps more importantly, the method for development of AUC is rigorous and does not permit alteration of the final scores and classification by the technical (rating) panel. Additionally, the AUC do not state that testing “must” be performed, only that it is reasonable given the clinical scenario and the available medical knowledge/experience. AUC are therefore not equivalent to a Class I clinical practice guideline.

Although the COURAGE nuclear substudy was underpowered to detect differences in treatment approaches, those subjects who experienced a reduction of ischemia on single-positron emission computed tomography myocardial perfusion imaging had a superior outcome, although this difference was lost when further risk adjusted. Therefore, we agree with the opinion of Dr. Sethi and colleagues that “routine RNI can be of use, if we can identify a subgroup of asymptomatic patients . . . who can benefit from revascularization.” This thereby allows the indication to be considered “appropriate” or reasonable in the parlance of AUC.

We agree that, in light of the newer trials, it may not be accurate to place patients with only the risk factor of diabetes into the high-risk category. However, based on available information, we believe that the rating by the technical panel was reasonable. We await additional information on the best way for risk assessment of patients and will certainly consider revising the AUC as new evidence becomes available. Thank you for your thoughtful comments.

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doi:10.1016/j.jacc.2009.09.026

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The Need for Sex-Specific Data Prior to Food and Drug Administration Approval

We read with great interest the recent paper by Hsich and Piña (1) that examined the many aspects in which we lack data for heart failure in women. We wholeheartedly agree that heart failure trials must include more women and must provide more sex-specific data, and we further believe that there must be evidence of net benefit in women before Food and Drug Administration approval for devices to be implanted in critically ill patients.

For example, the authors mention that the recent approval of the Thoratec HeartMate II (Thoratec Corporation, Pleasanton, California) will allow more implantation of ventricular assist devices in women and will provide prospective data through the Interagency Registry for Mechanically Assisted Circulation registry. However, the device was approved based on data from only 44 women, who constituted 23% of the overall study population. The Food and Drug Administration's Summary of Safety and Effectiveness Data for this device noted that the small number of women “makes it difficult to draw any conclusions regarding differences in safety profile of the device between men and women” (2). Even so, it is worrisome that women had an increased rate of some important adverse events, including a 3-fold higher incidence of stroke (18% vs. 6% in men) and trends toward a higher incidence of bleeding and infection events. These risks may be worthwhile if the device had proven benefit, but it is concerning that the device's success rate did not meet the pre-specified end point for success (2).

Therefore, we agree with the authors that a post-approval registry to collect data on outcomes in women for this device will provide needed information. However, requiring evidence of benefit in women before Food and Drug Administration approval for implanted devices would be an important step toward ensuring that we are providing safe care for women with heart failure.

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doi:10.1016/j.jacc.2009.08.053

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Reply

We appreciate the insightful remarks of Drs. Dhruva and Redberg on our paper (1). We agree that to improve health care for women,