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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## REFERENCE

1. Hendel RC, Berman DS, Di Carli MF, et al. ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 appropriate use criteria for cardiac radionuclide imaging: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine. J Am Coll Cardiol 2009;53:2201–29.
2. Young LH, Wackers FJ, Chyun DA, et al., for the DIAD Investigators. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes. The DIAD study: a randomized controlled trial. JAMA 2009;301:1547–55.
3. Frye RL, August P, Brooks MM, et al., for the BARI 2D Study Group. A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med 2009;360:2503–15.
4. Boden WE, O'Rourke RA, Teo KK, et al., for the COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356:1503–16.

# The Need for Sex-Specific Data Prior to Food and Drug Adminstration 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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## REFERENCES

1. Hsich EM, Piña IL. Heart failure in women: a need for prospective data. J Am Coll Cardiol 2009;54:491–8.
2. Summary of Safety and Effectiveness Data. PMA 060040. Thoratec HeartMate® II Left Ventricular Assist System (LVAS). April 2008. Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf6/P060040b.pdf. Accessed August 10, 2009.

## Reply

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

we need better reporting of sex-specific results, enrollment of women commensurate with the prevalence of disease, and evidence of net benefit before approval of therapy. The Thoratec HeartMate II (Thoratec Corporation, Pleasanton, California) is a perfect example of this dilemma. There was an under-representation of women in the trial and a trend toward more adverse events. However, the paucity of women prevented a final conclusion. Unfortunately, there was also no alternative life-saving therapy for small women when medical therapy failed and such patients needed long-term mechanical support to bridge them to transplantation. Even pulsatile mechanical devices have a higher incidence of neurologic events and bleeding in women compared with men, which further emphasizes the lack of alternative therapy and the need to better understand sex differences (2). The National Institutes of Health-sponsored Interagency Registry for Mechanically Assisted Circulation database will enable us to follow sex differences prospectively. Because the Thoratec HeartMate II is being used more extensively, the data will continue to accumulate, and sex-specific results will become available.

This dilemma is not unique to heart failure and must change to reduce the cardiovascular disease mortality rate in women. In a study by Blauwet et al. (3) that included 628 cardiovascular trials, only 24% provided sex-specific results. The highest percentage of reporting was in National Institutes of Health-sponsored studies (51% vs. 22%) and those published in general medicine journals when compared with cardiovascular journals (37% vs. 23%). Kim et al. (4) subsequently published a study concentrating on National Heart, Lung, and Blood Institute-funded cardiovascular phase 3 and 4 trials. The mean enrollment of women was lower than the percentage of women with that disease, and 6 of 19 trials did not even publish sex-specific results. This is a disappointment given the federal mandate that requires women and minorities to be included in phase 3 and 4 clinical trials in sufficient numbers to determine the effectiveness of a medical intervention (5).

The effectiveness of any therapy for women can be assessed only if sufficient numbers of women are included in clinical trials. We concur that it would be best to show benefit before approval of any new therapy and that following a post-approval registry is a suboptimal alternative. To make it easier to enroll more women, national organizations should launch educational campaigns to the public regarding the lack of evidence-based sex- and minority-specific therapy. Given the success of the Red Dress Campaign to increase awareness that women are more likely to die of cardiovascular disease than of breast cancer, a similar campaign requesting them to volunteer rather than wait to be approached may be beneficial.

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## REFERENCES

1. Hsich EM, Piña IL. Heart failure in women: a need for prospective data. J Am Coll Cardiol 2009;54:491–8.
2. Interagency Registry for Mechanically Assisted Circulation (INTERMAC). Available at: http://www.uab.edu/ctsresearch/intermacs/presentations.htm. Accessed September 8, 2009.
3. Blauwet LA, Hayes SN, McManus D, Redberg RF, Walsh MN. Low rate of sex-specific result reporting in cardiovascular trials. Mayo Clin Proc 2007;82:166–70.
4. Kim ES, Carrigan TP, Menon V. Enrollment of women in National Heart, Lung, and Blood Institute-funded cardiovascular randomized controlled trials fails to meet current federal mandates for inclusion. J Am Coll Cardiol 2008;52:672–3.
5. U.S. Congress Public Law No. 103-43. National Institutes of Health Revitalization Act of 1993. June 10, 1993.

# Noninferiority of Pitavastatin in Intravascular Ultrasound Findings

We read with interest the paper by Hiro et al. (1) comparing the regressive effect of pitavastatin on coronary plaque volume in acute coronary syndrome patients with that of atorvastatin using intravascular ultrasound (IVUS). The authors demonstrated that the upper limit of the 95% confidence interval of the difference in the mean percentage of change in plaque volume between the 2 groups (mean 1.11%, 95% confidence interval: −2.27% to 4.48%) did not exceed the pre-defined noninferiority margin of 5% and concluded that the noninferiority of pitavastatin compared with atorvastatin.

However, although an IVUS study comparing pravastatin with atorvastatin demonstrated a similar result (the difference in the mean percentage of change in atheroma volume was 1.3%, 5.4% in the pravastatin group and 4.1% in the atorvastatin group) (2), a clinical end point study (n = 4,162) using the same drugs demonstrated a significant difference in death or major cardiovascular event rates (26.3% in the pravastatin group and 22.4% in the atorvastatin group) (3). Therefore, it remains uncertain whether the noninferiority of pitavastatin in IVUS findings would translate to clinical noninferiority (4). Even such a small difference in IVUS findings may lead to a significant difference in clinical event rates in a large clinical trial.

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## REFERENCES

1. Hiro T, Kimura T, Morimoto T, et al. Effect of intensive statin therapy on regression of coronary atherosclerosis in patients with acute coronary syndrome: a multicenter randomized trial evaluated by volumetric intravascular ultrasound using pitavastatin versus atorvastatin (JAPAN-ACS [Japan assessment of pitavastatin and atorvastatin in acute coronary syndrome] study). J Am Coll Cardiol 2009;54:293–302.
2. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA 2004; 291:1071–80.