MACE was the abbreviation of “major adverse cardiovascular events.” In Table 4 and the related results part, MACE referred to “major adverse coronary events.” Furthermore, “major adverse cardiac events” appeared in the abstract and result part as another full name of MACE. According to the recommendation of the Academic Research Consortium (2), the term MACE can be device-oriented or patient-oriented. Without any definition and identical full name of MACE in the SESAMI trial, a formidable barrier was built to understanding the results and to comparison with other clinical trials.

My other concern is the inclusion criteria of the patients. In the Menichelli article (1), all the patients had AMI eligible for primary angioplasty, which seemed to be confirmed later in the catheterization and study procedure part. But in the slides presented by the author in EuroPCR 2006 (3), the rate of rescue coronary angioplasty accounted for 17.5% in the sirolimus-eluting stent (SES) group and 17.7% in the BMS group. The related information on rescue percutaneous coronary intervention in the study design and protocol should be described because it was a different treatment strategy for AMI patients.

By the way, the value of standard deviation of stent diameter in the SES group in Table 2 might be 0.34 instead of 0.034, according to the context.

"Xiaohong Pan, PhD, MD

*Department of Cardiology
2nd Affiliated Hospital, School of Medicine
Zhejiang University
Jiefang Road 88
Hangzhou, Zhejiang 310009
China
E-mail: heartpanxh@hotmail.com

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In designing the SESAMI (Sirolimus-Eluting Stent Versus Bare-Metal Stent in Acute Myocardial Infarction) trial, we tried to establish consistency among end point definitions. Indeed, this trial was among the first to adopt and utilize the new Academic Research Consortium definition of stent thrombosis—well before Dr. Cutlip’s article was published.

As far as inclusion criteria are concerned, all of the patients presented with ST-elevation myocardial infarction and were eligible for primary angioplasty. We adopted the same strategy for all the patients once they were in our catheterization laboratory; however, a small portion of them had previously received thrombolytic therapy, as reported in Table 1 of our original study (2).

Dr. Pan surmises correctly that decimal point was misplaced in the standard deviation value for the sirolimus-eluting stent diameter in Table 2 of our study (2). The correct value is 0.034.

"Maurizio Menichelli, MD

*San Camillo Hospital of Rome
via della Grande Muraglia 46
Rome 00144
Italy
E-mail: menichelli747@yahoo.com

doi:10.1016/j.jacc.2007.10.015

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Resting Heart Rate and Cardiovascular Disease: The Beta-Blocker–Hypertension Paradox

The hypothesis of Fox et al. (1) of heart rate being an independent predictor of cardiovascular and all-cause mortality in people with and without diagnosed cardiovascular disease is convincing and supported by a solid body of evidence. Considerably less well documented is that pharmacologic heart rate slowing within the physiologic range will reduce cardiovascular events or, indeed, increase longevity. As Fox et al. (1) point out, it is likely that the beneficial effect of beta-blockers after myocardial infarction and in congestive heart failure is, at least to some extent, related to a reduction in heart rate. However, the opposite seems to be true in hypertension: we recently found a greater risk of cardiovascular events or, indeed, increase longevity. As Fox et al. (1) point out, it is likely that the beneficial effect of beta-blockers after myocardial infarction and in congestive heart failure is, at least to some extent, related to a reduction in heart rate. However, the opposite seems to be true in hypertension: we recently found a greater risk of cardiovascular events (all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, and heart failure, all p < 0.0001) with a lower
heart rate in a meta-analysis of more than 60,000 patients in 9 large beta-blocker trials (2). Thus, the greater the heart rate reduction with beta-blockers, the greater the risk of cardiovascular events in hypertensive patients. The reason that drug-induced bradycardia is less beneficial than spontaneously occurring bradycardia may be related to the dysynchrony of the reflected pulse wave and the outgoing pressure wave. Ideally, the reflected wave should return toward the heart during diastole to augment diastolic filling. If the wave returns earlier during the cardiac cycle, as is the case with pharmacologic heart rate slowing, it amplifies the outgoing pressure wave, thereby increasing systolic pressure. Indeed, findings from the CAFÉ (Conduit Artery Function Evaluation) (3) study, in which pulse-wave analysis was used to derive central aortic pressure, documented a pseudo-antihypertensive effect of the beta-blocker regimen (4). Despite identical brachial pressure in both treatment arms, central aortic systolic pressure was lowered significantly less well with atenolol than with amlodipine. Thus, pulse-wave dysynchrony, secondary to heart rate slowing, may account for the beta-blocker-hypertension paradox. This would indicate that not all heart rate slowing is created equal—bradycardia induced by negative chronotropic drugs may not necessarily be as beneficial as bradycardia occurring spontaneously or being related to aerobic conditioning.

*Hypertension Program
Division of Cardiology
Columbia University College of Physicians and Surgeons
St. Luke’s-Roosevelt Hospital Center
1000 Tenth Avenue, Suite 3B-30
New York, New York 10025
E-mail: fmesserli@aol.com

Please note: Dr. Messerli is an ad hoc consultant/speaker for Abbott, GlaxoSmithKline, Novartis, Pfizer, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Forest, Daiichi Sankyo, Sanofi-Aventis, Merck, and King Pharmaceuticals.

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Reply

Resting heart rate is a strong predictor of cardiovascular and all-cause mortality in various populations, including hypertensive patients. Moreover, the strong relationship between heart rate reduction and mortality reduction has been robustly established by data on the effect of beta-blockers and, to a lesser extent, heart rate-reducing calcium-channel blockers in patients after myocardial infarction (MI) and with heart failure (HF) (1).

In their letter to the Journal, Drs. Messerli and Bangalore suggest that bradycardia induced by negative chronotropic drugs may not necessarily be as beneficial as bradycardia occurring physiologically and support the suggestion with the observation that blood pressure reduction with beta-blockers, which is associated with heart rate reduction, is less beneficial in minimizing cardiovascular outcome in hypertensive patients as compared with other non-heart rate slowing antihypertensive agents.

In contrast with post-MI or HF studies, the beta-blocker atenolol was the chronotropic drug used in most of the hypertension clinical trials reported by Drs. Messerli and Bangalore. By reducing heart rate and myocardial inotropism and increasing left ventricular (LV) ejection time, atenolol (like the majority of beta-blockers) alters the pattern of pulse-wave reflection. The increase in the augmentation index reported after beta-blockers results in increased central systolic blood pressure in hypertensive patients. Thus, beta-blockers could have a deleterious effect on LV-aortic coupling, LV afterload, LV hypertrophy, and, ultimately, the risk of cardiovascular events. The observations could explain the less-than-expected beneficial effect of atenolol on clinical outcome in the CAFÉ (Conduit Artery Function Evaluation) study (2) reported by Drs. Messerli and Bangalore.

However, although the pulse-wave dysynchrony observed with atenolol may account for the beta-blocker paradox and the increase in central blood pressure observed in hypertensive patients, we should be cautious about attributing the phenomenon to heart rate slowing per se. As previously mentioned, beta-blockers not only affect heart rate, they also reduce blood pressure and alter cardiac contractility, relaxation, systolic ejection time, and pulse-wave reflection.

An interesting point is that for a given reduction in a heart rate, the dysynchrony between the forward and the reflected pulse wave may not be the same for atenolol as for other beta-blockers. (3). In addition to the potentially deleterious effect of beta-blockers, as a group, on pulse-wave reflection for reasons unrelated to heart rate reduction, other issues might be considered in assessing the impact of beta-blockers, including, perhaps most importantly, the magnitude of heart rate reduction achieved in the individual trials or individual patients in the meta-analysis by Bangalore et al. (4), which may determine the extent to which any deleterious effects of beta-blockade might be obviated by heart rate slowing.

Therefore, the hypertension paradox observed with beta-blockers (mainly atenolol) cannot be solely explained by pharmacologic heart rate slowing, and findings should not be extrapolated to pharmacologic interventions aiming at pure heart rate reduction. In other words, the way in which one slows the heart rate may be important in determining the outcome of heart rate slowing. We all are aware, however, of the limitations of observational datasets, whether when suggesting benefit of a spontaneously “low” heart rate or possible harm from pharmacologic heart rate reduction with beta-blockers in hypertension. Fortunately, the hypothesis that heart rate lowering is beneficial clinically is being put to test in 2 large-scale outcome randomized clinical trials.

Kim Fox, MD, FESC
Jeffrey S. Borer, MD, FACC
A. John Camm, MD, FESC, FACC
Nicolas Danchin, MD, FESC
*Roberto Ferrari, MD, FESC