stress echocardiography study, patients with enlarged left atrium have 3.4 times the event rate of a normal LA size (0.5%/year vs. 1.7%/year). This might not merit further invasive workup. However, it does merit aggressive medical management of risk factors, because an event rate of 1.7%/year cannot be considered as benign as the same event rate in a mildly abnormal stress echocardiography study (wall motion score index 1.1 to 1.7) (12). Thus, we disagree with Dr. Farzaneh-Far and colleagues that LA size should not be incorporated into risk stratification. In echocardiography as in other imaging techniques, evaluating multiple parameters defines diagnostic and prognostic data more accurately. As stated in our article, “further studies using LA volumes are needed to elucidate the role of diastolic dysfunction in patients undergoing stress echocardiography and to further evolve the concept of diastolic stress echocardiography.”

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doi:10.1016/j.jacc.2007.10.019

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Beta-Blocker Therapy in Hypertension: A Need to Pause and Reflect

The recent State-of-the-Art Paper by Bangalore et al. (1) questioned the utility of betablockers as first-line treatment for “uncomplicated” hypertension. Although the authors indicate that they “do not want to throw the baby out with the bathwater,” we are concerned that the overall tone of the article is so negative that this indeed might happen. Thus, we believe that the following comments might be helpful when clinicians are deciding whether or not to use beta-blockers in a particular patient.

Bangalore et al. (1) cited a lack of benefit with beta-blockers in reducing all-cause or cardiovascular mortality and myocardial infarction from a meta-analysis by Lindholm et al. (2); in fact, no difference was observed for these end points versus other anti-hypertensives. Some of the early assessments of beta-blockers, including the STOP-1 and -2 (Swedish Trial in Old Patients with Hypertension-1 and -2), showed that beta-blockers reduced total and cardiovascular morbidity compared with placebo and that the results were similar to angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers (3,4).

Most of the evidence summarized by Bangalore et al. (1) concern studies of atenolol. However, the authors neglected to point out that the less favorable clinical outcomes seen with atenolol versus other therapies might be due to an absence of 24-h efficacy when it is used once daily at a dose of 50 mg. In fact, the INVEST (International Verapamil-Trandolapril Study) demonstrated no difference in outcomes between a beta-blocker- and calcium-antagonist–based regimen (5). Notably, in this trial atenolol was dosed twice daily. Similarly, data from the UKPDS (United Kingdom Prospective Diabetes Study) also showed atenolol to have efficacy similar to an ACE inhibitor regimen in preventing macrovascular complications in hypertensive diabetic patients (6).

We also believe that the term, “pseudo antihypertensive” efficacy, is misleading, because the authors probably refer to relative blood pressure reductions as distinct from the efficacy of treating the disease, hypertension. As the authors point out, beta-blockers are important for treating a wide range of high-risk cardiovascular conditions.

We agree with the authors that, historically, use of traditional beta-blockers has been constrained by associated side effects, in particular, fatigue and sexual dysfunction. However, there is mounting evidence showing that the side effect profile of vasodilatory beta-blockers is markedly different and comparable to placebo (7,8). Vasodilating beta-blockers also demonstrate neutral or beneficial metabolic profiles. As cited by the authors, the GEMINI (Glycemic Effects in Diabetes Mellitus: Carvedilol-
Metoprolol Comparison in Hypertensives) study in diabetic hypertensives showed maintained glycemic control and improved insulin resistance with carvedilol versus metoprolol (8). Similarly, nebivolol demonstrated improved insulin sensitivity when compared with metoprolol in hypertensive patients (9).

The authors incorrectly state that the European Society for Hypertension/European Society of Cardiology (ESH/ESC) is no longer endorsing beta-blockers as first-line therapy for hypertension. In actuality, ESH/ESC guidelines, published this year, maintain beta-blockers among the classes of drugs suitable for initiation and maintenance of blood pressure treatment (10). Furthermore, ESH/ESC and the American College of Clinical Endocrinologists recognize the differences that exist between agents in this class, distinguishing the vasodilatory beta-blockers from traditional ones in patients with metabolic risk factors.

We are not sure what the phenotype of an “uncomplicated” patient with hypertension is. Clearly, many with increased blood pressures have non-obstructive coronary and carotid plaques.

The use of beta-blockers in the treatment of patients with hypertension is deeply rooted in the knowledge of the role of the sympathetic nervous system in the pathophysiology of complications. We believe that recommendations for the use of beta-blockers in an individual with hypertension should be made after reviewing the totality of the data. Beta-blockers will continue to play a critical role in treatment of hypertension, and dismissing the entire class without fully examining the evidence might indeed amount to “throwing the baby out with the bath water.”

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doi:10.1016/j.jacc.2007.09.050

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We thank Dr. Giles and colleagues for their interest in our paper (1) and completely agree with their contention that “recommendations for the use of beta-blockers in the individual with hypertension should be made after reviewing the totality of the data.” Unfortunately, the totality in this case is completely negative. Ever since our meta-analysis about a decade ago, study after study has attested to the inefficacy of beta-blockers in hypertension. Why would any physician expose a hypertensive patient to a drug that reduces mortality no better than placebo, as evidenced in the thorough Cochrane meta-analysis (2), and yet leads to a withdrawal rate that is twice as high as the one seen with diuretics (which are certainly not the best-tolerated drug class for the treatment of hypertension)? We are puzzled by our colleagues’ cherry-picking of the STOP-1 and -2 (Swedish Trial in Old Patients with Hypertension-1 and -2). Neither of those studies dared to conclude that beta-blockers per se reduce morbidity and mortality. The reason for this is very simply that neither one analyzed the effects of diuretics and beta-blockers separately. Thus, STOP-1 and -2 studies are classical examples of gin-and-tonic studies in which about two-thirds of patients treated with a beta-blocker also received a thiazide diuretic.

The INVEST (International Verapamil-Trandolapril Study) is a landmark trial in which an atenolol (given mostly twice a day)-based regimen was compared with a verapamil-based regimen, as Dr. Giles and colleagues point out. However, all of the patients in the INVEST study had well defined coronary artery disease, and an extrapolation from such a high-risk population to uncomplicated hypertension is not appropriate. As can be seen in our Figure 3 (1) we are convinced that coronary artery disease is an acceptable indication for the use of beta-blockers.

We use the term pseudoantihypertensive efficacy to describe the observation in the CAFE (Conduit Artery Function Evaluation) study (3) that, for a given brachial blood pressure, atenolol lowered central aortic blood pressure significantly less than did amlodipine. Therefore, practicing physicians may wrongly conclude that beta-blockers per se reduce morbidity and mortality. The term pseudoantihypertensive efficacy aptly describes this phenomenon.

We certainly agree with our colleagues, and we have stated so (4), that vasodilating beta-blockers have a different hemodynamic profile and a different metabolic/endocrine profile, induce less weight gain (5), and are better tolerated than the traditional beta-blockers. Thus, nebivolol and carvedilol are not only better tolerated but also have the potential to be more beneficial in terms