

2. Dahlof B, Lindholm LH, Hansson L, Schersten B, Ekbom T, Wester PO. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet* 1991;338:1281-5.

Different Metabolic Effects of Selective and Nonselective Beta-Blockers Rather Than Mere Heart Rate Reduction May Be the Mechanisms by Which Beta-Blockade Prevents Cardiovascular Events

We read with interest the article by Bangalore et al. (1), who analyzed in 9 trials the role of pharmacologic reduction of heart rate (HR) using beta-blockers in preventing cardiovascular events in patients with hypertension. Beta-blocker-induced lower HR was associated with greater mortality and morbidity risk. As the basis of worse outcomes with “beta-blockers,” the authors recognize only an increase in central aortic/pulse pressure with pharmacologic HR lowering. Even though they acknowledge that the beta-blocker used in the studies was mainly atenolol, and hence, any extrapolation of these results to other beta-blockers should be done with caution, the whole paper and the accompanying editorial just generically refer to “beta-blockade.” In fact, the mechanisms by which beta-blockers improve prognosis in different cardiac contexts are probably multiple. Improved energy efficiency seen with some beta-blockers (2) could be one of the reasons for better survival observed with their use (3). Additionally, central inhibition of sympathetic activity with moxonidine in heart failure, despite a significant reduction of HR, has been associated with increased mortality (4). In fact, moxonidine has been shown to alter myocardial metabolism (5). This could be the reason for the failure of central sympathetic inhibition to prevent deaths in patients with heart failure and also indicates that the predominant mechanism of action of “effective” beta-blockers is probably related to mechanisms other than mere HR reduction. In fact, apart from reducing HR, atenolol and most selective beta-blockers impair endothelial function, decrease insulin sensitivity, and increase lipid levels (6), all conditions that may worsen the global risk profile. Conversely, new generation beta-blockers have been seen to improve metabolism and endothelial function (7). Therefore, HR reduction in itself, especially if associated with a bulk of deleterious metabolic and vascular effects, is definitely not enough to improve prognosis. The alarm created by the Bangalore et al. (1) paper should be clearly confined to selective beta-blockers and not generically extended to the whole drug class.

*Gabriele Fragasso, MD
Michela Cera, MD
Alberto Margonato, MD

*Istituto Scientifico San Raffaele, Milan, Italy
Clinical Cardiology-Heart Failure Clinic
via Olgettina 60
Milan 20132
Italy
E-mail: gabriele.fragasso@hsr.it

doi:10.1016/j.jacc.2008.12.075

REFERENCES

1. Bangalore S, Sawhney S, Messerli FH. Relation of beta-blocker-induced heart rate lowering and cardioprotection in hypertension. *J Am Coll Cardiol* 2008;52:1482-9.
2. Podbregar M, Voga G. Effect of selective and nonselective beta-blockers on resting energy production rate and total body substrate utilization in chronic heart failure. *J Cardiac Fail* 2002;8:369-78.
3. Poole-Wilson P, Swedberg K, Cleland J, et al., Carvedilol or Metoprolol European Trial Investigators. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet* 2003;362:7-13.
4. Wiltse C, Wright T, for the MOXCON Investigators. Adverse mortality effect of central sympathetic inhibition with sustained-release moxonidine in patients with heart failure (MOXCON). *Eur J Heart Fail* 2003;5:659-66.
5. Mobini R, Jansson PA, Bergh CH, Sharing Tang M, Waagstein F, Andersson B. Influence of central inhibition of sympathetic nervous activity on myocardial metabolism in chronic heart failure: acute effects of the imidazoline I1-receptor agonist moxonidine. *Clin Sci* 2006;110:329-36.
6. Lithell HO. Effect of antihypertensive drugs on insulin, glucose, and lipid metabolism. *Diabetes Care* 1991;14:203-9.
7. Celik T, Iyisoy A, Kursaklioglu H, et al. Comparative effects of nebivolol and metoprolol on oxidative stress, insulin resistance, plasma adiponectin and soluble P-selectin levels in hypertensive patients. *J Hypertens* 2006;24:591-6.

Beta-Blockers and Hypertension

Bangalore et al. (1) state that unlike results from post-myocardial infarction and congestive heart failure studies, a beta-blocker-induced low heart rate (HR) in hypertension is associated with an increase in death rate and cardiovascular (CV) events. This conclusion is highly misleading.

In post-myocardial infarction and congestive heart failure studies, the benefit from beta-1 blockade arises from decreased work of the heart (via reduced HR and blood pressure), reduced ventricular fibrillation risk, and a reduction in catecholamine-induced (beta-1) cardiac necrosis and apoptosis (2); thus, intrinsic sympathomimetic activity reduces efficacy (2). The situation with hypertension is complex, as diastolic hypertension in the young/middle-aged arises from a link with obesity (3) and high sympathetic nerve activity plus raised cardiac output (2). In contrast, isolated systolic hypertension arises in the elderly via a decrease in vascular compliance (3).

The 3 main contributor trials in the Bangalore et al. (1) study were the ASCOT (Anglo-Scandinavian Cardiac Outcomes), LIFE (Losartan Intervention for Endpoint Reduction in Hypertension), and INVEST (International Verapamil SR Trandolapril Study) studies in elderly patients with hypertension, which involved moderately beta-1 selective atenolol as the first-line choice. Atenolol does not improve vascular compliance (2), so it does not lower central systolic pressure; indeed first-line atenolol slightly increases central pressure (4), possibly linked to partial beta-2 block-