**EDITORIAL COMMENT**

**Beta-Blockers in Hypertension**

**Adding Insult to Injury**

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Beta-blockers have been found not to be effective for primary prevention of cardiovascular disease in patients with primary hypertension. The problem was first recognized by Messerli et al. (1) in 1998. They pointed out the significantly lesser benefit of beta-blocker therapy in 2 trials versus diuretic-based therapy in 7 separate trials. Their presentation could not have been clearer: “Diuretic therapy was superior to blockade with regard to all end points... β-blocker therapy only reduced the odds for cerebrovascular events but was ineffective for preventing coronary heart disease, cardiovascular mortality and all-cause mortality.”

This clear distinction was not referenced in the 2003 Joint National Committee (JNC) report (2), which favored a diuretic for first drug but indicated that beta-blockers were suitable alternatives, particularly when a “compelling” indication was present, including heart failure, post-myocardial infarction, high coronary disease risk, or diabetes mellitus.

A few months after the 2003 JNC report was published, Messerli et al. (3), with 3 well-established hypertension experts, said it again, even more clearly: “The time has come to admit that beta-blockers should no longer be considered appropriate for first-line therapy of uncomplicated hypertension.”

**The British and European Hedges**

Even after this indictment, however, the 2004 British Hypertension Society (BHS) guidelines (4) put beta-blockers alongside angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) as initial therapy for hypertensive patients under age 55 years and for nonblack patients. The 2004 BHS guidelines did, however, hedge their position, stating that according to their AB/CD algorithm, either an ACEI or an ARB (A) or a beta-blocker (B) should be chosen for younger and nonblack patients whereas either a calcium-channel blocker (C) or a diuretic (D) should be chosen for patients who are over age 55 years or black, but the algorithm does place the “B” in brackets. The report says, “the reason is to emphasize the fact that recent trials have reported an increase in onset of diabetes in patients treated with B or D drugs compared with A or C drugs, especially when B and D are combined. We advise caution when using B+D in patients at especially high risk of developing diabetes as for example, patients with a strong family history of type 2 diabetes, obesity, impaired glucose tolerance, features of metabolic syndrome or of South Asian and African-Caribbean descent” (4).

Note that the warning did not relate to the lesser benefit of beta-blockers in general, only to their propensity to bring out diabetes.

The British did amend their position in a statement on their website on June 28, 2006, providing a new algorithm without a B (beta-blocker) anywhere to be found and including the statement that “beta-blockers are no longer preferred as a routine initial therapy for hypertension” (5).

This good advice, however, did not get through to the writers of the 2007 European Society of Hypertension and European Society of Cardiology guidelines (6). They stated: “Beta-blockers may still be considered an option for initial and subsequent antihypertensive treatment strategies. Because they favor an increase in weight, have adverse effects on lipid metabolism and increase (compared with other drugs) the incidence of new-onset diabetes, they should not be preferred, however, in hypertensives with multiple metabolic risk factors including the metabolic syndrome...” (6).

**The Swedish Explosion**

Messerli et al. (7) said it again in 2007, in this Journal, adding a litany of side effects from beta-blockers, including: (1) precipitation of diabetes; (2) little effect on regression of left ventricular hypertrophy; (3) likely failure to improve endothelial function; (4) weight gain; and (5) decrease in exercise endurance.

To emphasize their position, they added: “For every myocardial infarction or stroke prevented in the Medical Research Council study (8), 3 patients treated with atenolol withdrew from the study secondary to impotence and another 7 withdrew because of fatigue” (7).

Despite the persistence of Messerli et al. (1), the beta-blocker atenolol was the fourth most prescribed drug in the U.S. in 2005, with 44 million prescriptions per year (7). It required 2 papers in the *Lancet* from 3 Swedish authors (9,10), with their accompanying editorials, to bring the issue to the currently almost unanimous agreement that beta-blockers are no longer an appropriate choice for initial or, as stated in the 2006 BHS addendum, subsequent therapy of uncomplicated hypertension. In retrospect, it took the exhortation of Messerli et al. (1) to set the stage but, perhaps with Americans being generally less accepted in the rest of

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

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the world these days, it took the Swedes to lower the curtain.

Rather surprisingly, in view of the prior analyses by Messerli et al. (1) showing equal protection against stroke by beta-blockers, the problem shown by the Swedish meta-analyses was lesser protection against strokes by beta-blockers.

**The Additional Blow**

The paper by Bangalore et al. (11) in this issue of the *Journal* adds another post-mortem explanation for the fall of beta-blockers, showing higher mortality associated with the slower heart rate they induce. Of interest, the fall in pulse rate is an obvious mechanism for the higher central blood pressure with beta-blocker–based therapy noted by Williams et al. (12) in the CAFE (Conduit Artery Function Evaluation) study. With this addition to the evidence, beta-blockers will surely remain as indicated for heart failure, for after myocardial infarction, and for tachyarrhythmias, but no longer for hypertension in the absence of these compelling indications.

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**Key Words:** beta-blockers • cardiovascular events • heart rate • hypertension.