Brief Communications

β-Blockers in Hypertension—The Emperor Has No Clothes: An Open Letter to Present and Prospective Drafters of New Guidelines for the Treatment of Hypertension

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Over the past decade, national and international guidelines have proposed beta-blockers to be used on an equal footing with diuretics for initial therapy of hypertension. This preferred status was supposedly based on evidence documenting a reduction in morbidity and mortality with beta-blocker therapy in hypertension. We systematically analyzed all available outcome studies and found no evidence that beta-blocker based therapy, despite lowering blood pressure, reduced the risk of heart attacks or strokes. Despite the inefficacy of beta-blockers, the incidence of adverse effects is substantial. In the MRC study, for every heart attack or stroke prevented, three patients withdrew from atenolol because of impotence, and another seven withdrew because of fatigue. Thus the risk/benefit ratio of beta-blockers is characterized by lack of efficacy and multiple adverse effects. Given that many thorough, prospective, randomized trials attest to efficacy and safety of diuretics, calcium antagonists, ACE inhibitors, and angiotensin receptor inhibitors, the time has come to admit that beta-blockers should no longer be considered appropriate for first-line therapy in uncomplicated hypertension. Am J Hypertens 2003;16:870–873 © 2003 American Journal of Hypertension, Ltd.

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β-Blockers have been used for the treatment of hypertension for four decades. Together with diuretics, they were considered to be on an equal footing for initial antihypertensive therapy by numerous authoritative sources who drafted national and international guidelines. This preferred status was supposedly based on solid evidence documenting a reduction in morbidity and mortality with β-blocker therapy in hypertension. A closer look at the available evidence as provided below is sobering and throws some doubt on the efficacy and safety of β-blockers in hypertension. We believe that various guideline committees should seriously reconsider their endorsement of these agents for first line therapy in uncomplicated hypertension.

1. Medical Research Council (MRC) studies. In both MRC studies, β-blockers failed to significantly reduce cardiovascular morbidity and mortality. In fact the stroke rate was two to four times higher in patients receiving β-blockers than in patients on thiazide diuretics and not different from those receiving placebo. The only benefit demonstrated was a small reduction in strokes (0.9 per 1000 patients per year, \( P < .03 \)) in nonsmokers <65 years of age. This reduction was significant in men only.

2. The Heart Attack and Primary Prevention in Hypertension Trial (HAPPHY) and Metropolol Atherosclerosis Prevention in Hypertensives (MAPHY) studies. The HAPPHY trial, carried out only in men <64 years of age, showed no significant differences between the β-blocker and the diuretic arms. The MAPHY trial, an extension of the HAPPHY trial, showed an unexpected increase in coronary and total mortality in smokers treated with a diuretic. These findings were extensively criticized and the results of MAPHY seem to be of questionable validity.
3. The Swedish Trial in Old Patients with Hypertension (STOP)\textsuperscript{9} and the Coope and Warrender study.\textsuperscript{10} Although the majority of patients were started on a \( \beta \)-blocker, more than 60\% ended up receiving a \( \beta \)-blocker and diuretic in combination. The primary investigators of both of these studies clearly stated that no conclusion can be drawn with regard to monotherapy of the individual drugs. Thus Coope and Warrender state, “Since patients were not randomised to different treatment groups, it is impossible to compare response to the \( \beta \)-blocker and the diuretic.”\textsuperscript{10} These statements did not prevent misclassification of these studies as \( \beta \)-blockers studied in meta-analyses\textsuperscript{11} that subsequently were widely quoted as evidence for the efficacy of \( \beta \)-blockers. Indeed, the authors of the Sixth Report of the Joint National Committee based their treatment recommendation on this meta-analysis. The lead author of this meta-analysis concluded in 1997 that “the available scientific evidence provides strong support for diuretics and \( \beta \)-blockers as first-line agent.” Despite that, however, most recently there has been no new outcome evidence with regard to \( \beta \)-blockers in hypertension. The same authors, providing us with an updated meta-analysis in the same journal, concluded that “for uncomplicated hypertension, \( \beta \)-blockers should be considered a second-line antihypertensive agent.”\textsuperscript{12}

4. The International Primary Prospective Prevention Study in Hypertension (IPPPSH)\textsuperscript{13} trial. In the IPPPSH trial, \( \beta \)-blockers (oxprenolol) therapy was compared against therapy without a \( \beta \)-blocker. Of those patients receiving the \( \beta \)-blocker, 67\% also were taking a diuretic. Blood pressure (BP) was significantly lower in the \( \beta \)-blocker arm, and the IPPPSH study therefore cannot be classified as a comparison of \( \beta \)-blockers against a diuretic.

5. Cerebrovascular Disease. The effects of atenolol on secondary prevention of stroke and on secondary cerebroprotection was established in two multicenter, placebo-controlled trials including 372 and 1473 patients, respectively.\textsuperscript{14,15} In neither one of these trials did atenolol reduce fatal and nonfatal stroke, prevent myocardial infarction, or prevent any other cardiovascular event despite a significant fall in BP compared with placebo. However, despite the complete inefficacy of atenolol, adverse effects and withdrawal because of adverse effects were 49\% and 70\%, respectively, more common with atenolol than with placebo.

6. The United Kingdom Prospective Diabetes study (UKPDS).\textsuperscript{16} In the UKPDS study, \( \beta \)-blocker therapy was similarly efficacious in diabetic hypertensive patients (who are at a two- or threefold higher risk of cardiovascular disease than are patients with uncomplicated hypertension) as the ACE inhibitor captopril. Of note, six times more of these patients died of coronary heart disease than of strokes. However, there was no difference in fatal or nonfatal myocardial infarction, angina, or sudden death between the two treatment strategies despite the fall in BP.

7. The Losartan Intervention for Endpoint Reduction in Hypertension Study (LIFE)\textsuperscript{17} trial. In the LIFE study, atenolol was compared with losartan in patients with left ventricular hypertrophy. With the exception of myocardial infarction, an angiotensin receptor blocker was found to be consistently superior to \( \beta \)-blocker therapy alone or in combination in hypertensives and hypertensive diabetics, with 25\% fewer strokes and superior reduction of left ventricular hypertrophy. In patients with isolated systolic hypertension, the stroke risk was reduced by 40\% with losartan compared with atenolol.\textsuperscript{18}

8. \( \beta \)-Blockers and diuretics in combination. Whenever a \( \beta \)-blocker was added to diuretic therapy in the MRC-2 study, the benefit diminished and vanished completely with \( \beta \)-blocker monotherapy.\textsuperscript{19} This was true for all cardiovascular events, coronary events, all-cause mortality, and to a lesser extent also for strokes. In the Systolic Hypertension in the Elderly Program (SHEP)\textsuperscript{20} study, the addition of a \( \beta \)-blocker to the diuretic provided no additional benefit. As stated by Kostis et al, “Additional (independent) benefits attributable to atenolol or to reserpine were not identified.”\textsuperscript{21}

9. Ancillary evidence from effects on surrogate endpoints. Compared with other drugs or drug classes, \( \beta \)-blockers are least efficient in reducing left ventricular hypertrophy\textsuperscript{22,23} and vascular hypertrophy.\textsuperscript{24,25} \( \beta \)-Blockers have been shown to cause systematic weight gain,\textsuperscript{26} to increase the risk of developing de novo diabetes,\textsuperscript{27} and to have unfavorable effects in patients with metabolic syndrome.

10. Adverse effects. Compared with other drugs, \( \beta \)-blockers have a long list of side effects, including lethargy, reduced exercise capacity, sleep disturbance, vivid dreams, cold hands and feet, and also a reduction in peak expiratory flow rates. The MRC study\textsuperscript{3} allows us to calculate that for every heart attack or stroke prevented, three patients withdrew from the study because of impotence and another seven withdrew because of fatigue.\textsuperscript{28} This is hardly an acceptable risk/benefit ratio for a completely asymptomatic disease such as mild essential hypertension.

Thus, apart from very mildly hypertensive middle-aged British male nonsmokers, the evidence of \( \beta \)-blockers to reduce morbidity or mortality is either meager or nonexistent. Some of the above studies, particularly the MRC,
have been criticized because of high withdrawal rates and other pitfalls. However, accepting this criticism would invalidate these studies. Thus, with respect to reduction of events with \( \beta \)-blockers in hypertension, either there is evidence of absence, or absence of evidence—take your pick!

It is not our intention to doubt the efficacy of \( \beta \)-blockers in patients who have experienced an acute myocardial infarction,\(^{29,30}\) have angina, are in congestive heart failure,\(^{31}\) or have obstructive cardiomyopathy. Numerous thorough prospective, randomized trials have established efficacy of \( \beta \)-blockers beyond any doubt for these indications. Indeed, the recent JNC 7 guidelines\(^ {32}\) appropriately consider congestive heart failure and secondary cardioprotection in hypertensive patients an indication for the use of \( \beta \)-blockade. Moreover, it must be clearly emphasized that all outcome studies showing no benefit in hypertension were carried out with traditional \( \beta \)-blockers, such as atenolol and metoprolol. Conceivably, newer vasodilating agents such as lisoprolol and carvedilol, which have a more favorable hemodynamic profile, may be more beneficial. This view is supported by the recent Carvedilol or Metoprolol European Trial (COMET) study in congestive heart failure, in which carvedilol was superior to metoprolol in reducing morbidity and mortality.\(^ {33}\) Apart from congestive heart failure and coronary artery disease, \( \beta \)-blockers may be useful as add-on therapy in certain selected hypertensive patients. However, to extrapolate from these indications to first-line therapy for uncomplicated hypertension is not appropriate.\(^ {34,35}\)

Clearly, the time has come to admit that the emperor has no clothes and, mutatis mutandis, that \( \beta \)-blockers should no longer be considered appropriate as first-line therapy in the treatment of uncomplicated hypertension. This brings us back to the Hans Christian Andersen fairy tale “The Emperor’s New Clothes.” As the reader may remember, the emperor was parading through the streets of the city to show off to an admiring crowd his celebrated “new clothes.” Suddenly a small child cried out, “But the Emperor has nothing on!” And the Emperor stiffened for he knew it was true. “Nonetheless,” he thought, “the procession must go on.” And so he continued to walk, holding himself more proudly than ever while the chamberlains held up a train made of cloth that had never been there at all!”\(^ {35}\)

### References