Beta-blockers and diuretics in antihypertensive therapy: the debate continues

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Editor's note: In the April 2000 issue, Dr. Franz Messerli published an article entitled "Antihypertensive therapy: beta-blockers and diuretics—why do physicians not always follow guidelines?" *BUMC Proceedings* published commentaries to this article by Dr. Marvin Moser of Yale University School of Medicine and Dr. Norman Kaplan of The University of Texas Southwestern Medical Center at Dallas. Here, Dr. Messerli responds to those commentaries.

Statement: *In the British Medical Research Council (MRC) trial in the elderly, "The large number of dropouts greatly reduced the statistical power of the trial to show benefit. In the other trials, both in the young and the elderly, it is difficult to determine specific outcome. . . ."*
Response: It is certainly open to debate whether the MRC trial in the elderly allows a firm conclusion regarding the efficacy of beta-blockers. Despite the fact that blood pressure was lowered to exactly the same extent as with diuretics, beta-blockers conferred no morbidity or mortality benefits (1). Unfortunately, as Dr. Moser states, this is the only trial in which a beta-blocker arm was compared against a diuretic arm and against placebo. There are no other trials. Depending on the point of view, this means very simply that either there is no valid evidence for efficacy of beta-blockers or that the evidence available shows inefficacy of the beta-blockers. Thus, we are dealing either with absence of evidence or evidence of absence—take your pick!

Statement: *"In making the case for not using beta-blockers, Dr. Messerli ignores the fact that the use of beta-blockers reduces the incidence of strokes and congestive heart failure in both young and elderly patients. In addition, the use of beta-blockers, in both the young and elderly, in patients with or without diabetes, has been effective in reducing morbidity and mortality in patients postmyocardial infarction."*
Response: There are no data showing that beta-blocker monotherapy reduces the incidence of strokes and congestive heart failure. In both the Swedish Trial in Old Patients with Hypertension and the Coope and Warrender study, >60% of the patients were receiving a diuretic in combination with the beta-blockers, and the results were never reported separately for beta-blockers and diuretics (2, 3). It is more than likely that all benefits observed were due to diuretic therapy and that beta-blockers (as tonic water in gin and tonic) were merely an innocent bystander. The fact that beta-blockers remain a cornerstone in the management of the postmyocardial infarction patient allows no conclusion regarding their efficacy in the elderly patient with hypertension.

Statement: *"When added to 'usual therapy,' which includes diuretics, angiotensin-converting enzyme (ACE) inhibitors, and digitalis, these agents also have reduced the incidence of congestive heart failure, hospitalizations, and overall mortality."*
Response: There are no data showing that the *addition* of beta-blockers confers any benefit per se. In the MRC trial, whenever a beta-blocker was added to the diuretic, the benefits of diuretic therapy were substantially diminished and became completely nonsignificant with beta-blocker monotherapy (1). In an analysis of the Systolic Hypertension in the Elderly Program study, Dr. Kostis clearly stated, "Additional (independent) benefits attributable to atenolol or to reserpine were not identified" (4). The Cardiac Insufficiency Bisoprolol Study II, which Dr. Moser quotes, was not carried out in hypertensive patients (5).

Statement: *"Dr. Messerli ignores a great deal of science when he states that 'millions of elderly hypertensive patients are needlessly exposed to the cost, inconvenience, and adverse effects of beta-blockers.'"*
Response: Dr. Moser is much more experienced in studying science than I am; however, I wish he would provide us with the references of the studies that I ignored.

Statement: *"In the other trial [Captopril Prevention Project], a similar reduction in cardiovascular events was noted in a beta-blocker–based compared with an ACE inhibitor–based treatment program."*
Response: In the Captopril Prevention Project trial, captropril was compared with conventional therapy which was *not* a beta-blocker–based treatment but consisted of either diuretics, diuretics and beta-blockers, or beta-blockers (6). This is a classic example of "gin-and-tonic" thinking!

Statement: *"Patients with hypertension appear to have a higher incidence of renal cell carcinoma regardless of therapy." "Others find increased cancers in hypertensive patients regardless of therapy."*

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Response: The link between diuretic therapy and renal cell carcinoma has been established by no less than 10 case-control studies and 3 cohort studies in >1 million patients. Not a single study showed a lower risk of renal cell carcinoma in patients who were on a diuretic compared with those who were not. Statisticians and epidemiologists certainly can control these findings for "the presence of hypertension." However, as clinicians, Dr. Moser and Dr. Kaplan know that such a correction is virtually impossible. Any patient who has been hypertensive for >25 years has received diuretics in one form or the other—most often in fixed combinations. Thus, the common denominator between the incidence of renal cell carcinoma and hypertension is very likely diuretic therapy. Besides, what are the pathophysiologic mechanisms by which hypertension should cause renal cell carcinoma?

Statement: *"Dr. Messerli might pause to reflect on the reserpine cancer scare based on case-control and retrospective studies."*
Response: A thorough review of these 14 case-control studies revealed a statistically highly significant risk (odds ratio, 1.25; confidence interval, 1.09–1.44) (7). However, this is a good example of case-control studies being statistically significant but clinically not meaningful because the risk is small and reserpine is no longer used.

Statement: *"It may take as long as 15 to 20 years to develop this tumor [renal cell carcinoma], but some evidence should have been uncovered in careful follow-up studies of the >50,000 people who have participated in the diuretic treatment trials."*

Response: A reference concerning this cohort of 50,000 people and specific information regarding follow-up, clinical parameters, annual examination, etc. would be greatly appreciated. Who are these patients, who are their controls, and how are they screened for renal cell carcinoma? Diuretic therapy is a much less powerful risk factor for renal cell carcinoma than is cigarette smoking for lung cancer. Yet, one would not expect to see an increased incidence of cancer whenever the duration of exposure was <10 to 15 years.

1. Medical Research Council trial of treatment of hypertension in older adults: principal results. MRC Working Party. *BMJ* 1992;304:405–412.
2. Dahlöf B, Lindholm LH, Hansson L, Scherstén B, Ekbom T, Wester PO. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet* 1991;338:1281–1285.
3. Coope J, Warrender TS. Randomised trial of treatment of hypertension in elderly patients in primary care. *Br Med J (Clin Res Ed)* 1986;293:1145–1151.
4. Kostis JB, Berge KG, Davis BR, Hawkins CM, Probstfield J. Effect of atenolol and reserpine on selected events in the systolic hypertension in the elderly program (SHEP). *Am J Hypertens* 1995;8(12 Pt 1):1147–1153.
5. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;353:9–13.
6. Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, Luomanmaki K, Dahlof B, de Faire U, Morlin C, Karlberg BE, Wester PO, Bjorck JE. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 1999;353:611–616.
7. Messerli FH, Grossman E, Goldbourt U. Antihypertensive therapy and the risk of malignancies. Presented at the meeting of the International Society of Hypertension, Chicago, Ill, August 20–24, 2000.