Trends in Antihypertensive Drug Treatment

To the Editor:

It is disappointing to read once again that “β-blockers and thiazide diuretics are the only antihypertensive agents that have been shown to reduce cardiovascular mortality.”1 In these days of evidence-based medicine, we must ask: where is the evidence for this statement? The basic data referenced by Wang et al1 are those of the meta-analysis of Psaty et al,2 which are also shown in the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Yet, Figure 6 in the report shows very clearly that cardiovascular and total mortality are not reduced by β-blockade; the confidence intervals in both cases clearly overlap unity and are therefore not significant. Likewise, coronary heart disease is also not reduced by β-blockade, although stroke and congestive heart failure are. In contrast, all these end points are clearly reduced by low-dose diuretics. In another meta-analysis that focused on the elderly, diuretics but not β-blockers reduced cardiovascular mortality.3 It is difficult to understand why Wang et al included the Metoprolol Atherosclerosis Prevention in Hypertension (MAPHY) study as evidence for the benefits of β-blockade. This was an open-label, unblinded study without placebo control.

A further implication of the article by Wang et al is that calcium-channel blockers do not reduce cardiovascular mortality. However, in the Systolic Hypertension in Elderly in Europe (SYST-EUR) study of elderly patients with systolic hypertension, the dihydropyridine nitrendipine was particularly efficacious in diabetic patients, in whom cardiovascular mortality was strikingly reduced (odds ratio, 0.24; P = 0.02); their total mortality was also reduced (odds ratio, 0.45; P = 0.04).4 Less strong is the evidence from the Systolic Hypertension in Elderly Chinese Trial (SYST-CHINA), in which nitrendipine reduced both all-cause and cardiovascular mortality by 39% in elderly Chinese patients with systolic hypertension.5 Here, the protocol had a flaw. Although blinded and placebo-controlled, there was sequential rather than random allocation of treatment. Thus, the blinding was single rather than double.

Response

Our study’s objective was to investigate the journal advertising of antihypertensive medications as a potential reason that physicians fail to adhere to existing clinical guidelines. We think that discrepancies between current prescribing practices and the recommendations of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure deserve an explanation. Although the synthesis of comparative information on drug selection is an admittedly complex undertaking, this group continues to advocate diuretics and β-blockers as first-line therapy.1 Our finding that advertising for calcium-channel blockers increased during a time period when physicians prescribed fewer diuretics and β-blockers raises questions about the relative impact of drug promotion and clinical guidelines.

Dr Opie correctly notes that in the meta-analysis by Psaty et al2 cardiovascular mortality was reduced by diuretics but not by β-blockers. In one of the trials included in this meta-analysis, however, treatment consisting primarily of β-blockers as first-line therapy was associated with significant reductions in the primary cardiovascular end points, as well as overall mortality.3 Psaty et al’s2 meta-analysis dealt solely with placebo-controlled trials. Several trials directly comparing diuretics with β-blockers were excluded; these trials were performed after it was known that diuretics lowered total mortality in patients with hypertension. The Metoprolol Atherosclerosis Prevention in Hypertension (MAPHY) study, for instance, showed reductions in both total and cardiovascular mortality with β-blockers compared with diuretics.4 No trial showed β-blockers to be inferior to diuretics. Although the MAPHY results have been questioned because of its open-label design, it seems reasonable to conclude that β-blockers are at least equivalent to diuretics in terms of clinical outcome.

With respect to calcium-channel blockers, Dr Opie notes that nitrendipine was efficacious in diabetic patients in the Systolic Hypertension in Elderly in Europe (SYST-EUR) study. Neither total mortality nor cardiovascular mortality were reduced in the overall study population, however. Furthermore, another long-acting dihydropyridine was possibly associated with a higher incidence of fatal and nonfatal myocardial infarctions in diabetics in the Appropriate Blood Pressure Control in Diabetics (ABCD) study.5

Completion of the National Heart, Lung, and Blood Institute’s Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) may help resolve the uncertainty regarding drug selection in hypertension treatment. Until that time, current national guidelines suggest diuretics and β-blockers as first-line therapy.1 Our study grew from an attempt to explain why physicians fail to adhere to these guidelines. We noted that advertising for calcium-channel blockers increased contemporaneously with the declining use of diuretics and β-blockers, a finding consistent with an influence of drug promotion on prescribing.

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