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**Study concept and design:** Li, Dixon, Prakash, Lam, Garg.

**Acquisition, analysis, or interpretation of data:** Li, Dixon, Prakash, Kim, Knoll, Lam, Garg.

**Drafting of the manuscript:** Li, Prakash, Lam, Garg.

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## COMMENT & RESPONSE

### Guidelines for Managing High Blood Pressure

**To the Editor** Some evidence against  $\beta$ -blockers<sup>1</sup> has been published in recent years; however, the exclusion of these drugs as initial treatment of uncomplicated hypertension in the report from the panel members appointed to the Eighth Joint National Committee (JNC 8)<sup>2</sup> is surprising.

First, the evidence against atenolol was presented in only 1 study, the Losartan Intervention for Endpoint Reduction in Hypertension Study (LIFE),<sup>3</sup> and the quality of this evidence was classified as weak by the panel. Results from LIFE cannot be extrapolated to the general population because the patients included were a high-risk sample with ventricular hypertrophy by electrocardiography and a high prevalence of diabetes mellitus (13%) and cardiovascular disease (25%). Also, the mean age in LIFE was 66.9 years, and it has been shown that  $\beta$ -blockers can be more effective in patients with hypertension who are younger than 60 years.<sup>4</sup> In other studies that analyzed a general population, the performance of  $\beta$ -blockers was similar to that of other drugs or the evidence was not sufficient to draw conclusions.

Second,  $\beta$ -blockers differ substantially in their pharmacological properties in ways that may affect their relative efficacy and tolerability. Limitations of atenolol cannot be extrapolated to third-generation  $\beta$ -blockers (eg, carvedilol and nebivolol), which combine antihypertensive and vasodilatory properties. There are currently no mortality and cardiovascular event data on these vasodilating  $\beta$ -blockers as initial therapy for hypertension.<sup>1</sup>

Third, in clinical trials, atenolol is typically a once-daily therapy. However, this regimen may not provide a full 24 hours of blood pressure (BP) control. This bias may explain, in part, the reduced benefit in prevention of cardiovascular events attributed to atenolol compared with other antihypertensive agents.<sup>5</sup>

If the majority of patients with hypertension will require 2 or more drugs to achieve control of their hypertension, the concern about what antihypertensive drug should be used first becomes less urgent. Instead, we suggest prioritizing the study of combinations of antihypertensive drugs according to age, weight, cost, availability, and other variables.

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**To the Editor** The guideline from the panel appointed to the JNC 8<sup>1</sup> recommended drug treatment to lower BP for patients aged 60 years or older with systolic blood pressure (SBP) of 150 mm Hg or greater or diastolic blood pressure (DBP) of 90 mm Hg or greater. For patients younger than 60 years, the panel recommended medications for DBP of 90 mm Hg or greater. Both of these recommendations were classified as Grade A, presumably based on randomized clinical trials (RCTs). However, a systematic review that we coauthored in the *Cochrane Database of Systematic Reviews*<sup>2</sup> found no evidence supporting drug treatment for patients of any age with stage 1 (mild) hypertension (SBP of 140-159 mm Hg, DBP of 90-99 mm Hg, or both) and no previous cardiovascular disease (ie, primary prevention).

For the threshold recommendation for drug treatment for patients aged 60 years or older, the JNC 8 panel cited 6 RCTs. The first 3 were placebo-controlled RCTs (HYVET, Syst-Eur, SHEP) that only included patients with stage 2 hypertension (SBP  $\geq$ 160 mm Hg) rather than stage 1 hypertension. Although RCTs of patients with stage 2 hypertension confirm the effect of drugs for patients with stage 2, they should not be extrapolated to people with mild hypertension. The other 3 RCTs (JATOS, VALISH, and CARDIO-SIS) included almost exclusively patients with stage 2 hypertension and had no placebo control groups. Without a no-treatment group, these studies say nothing about the benefits and harms of drugs for low-risk patients with mild hypertension.

For patients younger than 60 years, the JNC 8 authors referenced 5 RCTs as providing “high-quality evidence” to support their strong (Grade A) recommendation for drug use above a DBP threshold of 90 mm Hg. All these trials mixed the results of patients with stage 1 and 2 hypertension. Of these trials, our Cochrane review included the Medical Research Council’s trial of drug treatment of mild hypertension,<sup>3</sup> the Australian Therapeutic Trial in Mild Hypertension,<sup>4</sup> and the VA Cooperative Study<sup>5</sup> because we could obtain individual patient data on treatment and outcomes. Among the patients representing primary prevention with mild hypertension from these trials, there was no proven benefit of drug treatment.

To be accurate, the latest guidelines for the thresholds for drug treatment should change the strength of the recommen-

dation to Grade E (“expert opinion”). Better still, the threshold for drug treatment recommendation should be changed to stage 2 hypertension (SBP  $>$ 160 mm Hg and DBP of 100 mm Hg), for which the strength could be appropriately graded as A.

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**To the Editor** The updated 2014 guidelines for the management of high BP in adults by the panel appointed to the JNC 8<sup>1</sup> did not consider issues relevant to sex differences in hypertensive health. Variables of age and race were addressed, but stratification by sex was omitted. Sex is a determinant of health outcomes, with differences in metabolism, hormonal milieu, pharmacodynamics, pathophysiology, and therapeutic considerations.

The issue of therapeutic options stratified by sex is of clear importance. Although some controversy remains regarding fetal teratogenicity of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), given the degree of irreversible risk, this needs to be a consideration when choosing pharmacological options for women at risk of becoming pregnant. According to the European Consensus Guidelines for the management of hypertension, “In women with child-bearing potential, ACE inhibitors and angiotensin receptor blockers should be avoided, due to possible teratogenic effects.”<sup>2</sup>

In addition, Bullo et al<sup>3</sup> stated, “Thirty years after the first description of ACE-I fetopathy, relevant complications are, at present, regularly described, indicating that the awareness of the deleterious effect of prenatal exposure to drugs inhibiting the renin-angiotensin system should be improved.” Until such time as there is definitive evidence of safety during preg-