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Author Contributions: Mr Li and Dr Garg had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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.
Critical revision of the manuscript for important intellectual content: Li, Dixon, Kim, Knoll, Lam, Garg.
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Study supervision: Garg.

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COMMENT & RESPONSE

Guidelines for Managing High Blood Pressure

To the Editor Some evidence against β-blockers[1] 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)[2] is surprising.

First, the evidence against atenolol was presented in only 1 study, the Losartan Intervention for Endpoint Reduction in Hypertension Study (LIFE),[3] 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 β-blockers can be more effective in patients with hypertension who are younger than 60 years.[4] In other studies that analyzed a general population, the performance of β-blockers was similar to that of other drugs or the evidence was not sufficient to draw conclusions.

Second, β-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 β-blockers (eg, carvedilol and nebivolol), which combine antihypertensive and vasodilatory properties. There are currently no mortality and cardiovascular event data on these vasodilating β-blockers as initial therapy for hypertension.[1]

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.[5]

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[1] 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*[2] 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 ≥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,[3] the Australian Therapeutic Trial in Mild Hypertension,[4] and the VA Cooperative Study[5] 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 recommendation 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[1] 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."[2]

In addition, Bullo et al[3] 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-

nancy, caution must be taken, particularly because effective alternatives can easily be used.

Women with hypertension are less likely to be treated to goal,[4] presumably contributing to the excess cardiovascular disease observed in women compared with men.[5] Because tests of heterogeneity in RCTs fail to demonstrate sex differences in outcomes, hypertension guidelines should reinforce that evidence-based guideline therapy should be equally applied to both women and men. Hypertension management cannot be optimized if sex-specific therapeutic considerations are omitted from clinical guidelines.

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In Reply Dr Morales-Salinas and colleagues raise concerns about the panel's decision to exclude β-blockers as first-line therapy for hypertension, which was driven by the results of LIFE.[1] The evidence quality was graded low because it was based on 1 study with a population limited to individuals with hypertension and left ventricular hypertrophy by electrocardiogram. We agree that atenolol may have less favorable properties than some of the newer β-blockers, but the latter have not been well studied in comparative RCTs. In other studies, β-blockers performed similarly to the comparator drugs or the evidence was insufficient. This is an example in which the evidence is not clear-cut. In light of such uncertainty, the panel relied on predefined rules for making decisions. After review of the evidence and discussions about issues such as those raised by Morales-Salinas and colleagues, the panel voted to exclude β-blockers as initial therapy. However, the vote was not unanimous, which is not surprising given that diverse panel members may draw different conclusions when presented with evidence that is uncertain and requires interpretation. We believe the guideline enhances the understanding of how to apply clinical trial evidence in the uncertain world of clinical practice by explicitly clarifying which recommendations are supported by evidence and which are opinion-based.

Dr Cundiff and colleagues argue that mild hypertension should not be treated with drugs and that the recommendation to treat to a SBP goal of less than 150 mm Hg should instead be less than 160 mm Hg. Rather than restate the panel's rationale (question 1 and 2 evidence statements in the online supplement for the article), which we assert is evidence based, we acknowledge that there is controversy regarding the SBP goal in this population. Although the evidence did support a different BP threshold for initiating treatment (<160 mm Hg), the panel supported using the goal BP as both the threshold and goal for treatment. After review of the evidence and many discussions, a supermajority of the panel supported a goal of less than 150 mm Hg based on the clear benefits demonstrated in the 3 RCTs that treated patients with a goal of less than 150 mm Hg[2-6] and the lack of benefits seen in the other trials that treated to a lower goal.

We agree with the comments of Dr Klein and colleagues regarding the importance of sex as a determinant of health outcomes and that differences in pathophysiology, pharmacodynamics, metabolism, and hormones may require special consideration regarding therapeutic options. However, due to resource constraints and the rigorous nature of the evidence review, the panel had to limit the search to 3 of 23 original questions. The review did not find any studies that demonstrated sex-related differences on important health outcomes; thus, the panel could not make evidence-based recommendations that differed for women. However, that does not diminish the importance of this topic. More research is needed to delineate the differences in sex-specific management options. We also agree that fetal teratogenicity of ACE inhibitors and ARBs is an important issue, and these agents should not be used by women who might become pregnant.

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Medtronic, Merck, Novartis, and Takeda Global Research and Development; individual payment for lectures from Daiichi Sankyo, Merck, Novartis, and Pfizer; individual and institutional payment for development of educational presentations from ASH/AHSR (Daiichi Sankyo); and individual and institutional payment from Amarin Pharma, Daiichi Sankyo, and LipoScience for educational grants for the annual University of Alabama at Birmingham Vascular Biology and Hypertension Symposium. No other disclosures were reported.

Disclaimer: The views expressed do not represent those of the National Heart, Lung, and Blood Institute or the federal government.

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Interpreting Whole-Genome Sequencing

To the Editor We believe that the report of the yield and interpretability of clinical whole-genome sequencing by Dr Dewey and colleagues[1] is unduly pessimistic about the present and future efficacy of this molecular genetic technology in clinical medicine. Their experience of low coverage of key disease genes, poor nucleotide-calling reproducibility, low diagnostic yield, and insurmountable interpretative challenges for unexpected variants is at odds with that of most centers offering clinical genomic sequencing,[2] including our own.

Aside from possible technical problems unique to their laboratory, which we cannot judge from outside, they may have preordained their discouraging results by setting up a number of straw men that do not reflect the state of clinical genomic testing elsewhere, such as the use of whole-genome rather than whole-exome sequencing, the targeting of a healthy rather than syndromically affected cohort of patients, and the focus on adults rather than children, which limits the ability to include parents in the testing (trio) to greatly simplify variant filtering and interpretation.

In contrast to the 12 patients reported, robust clinical experience is already available, and when performed under alternative conditions, this technology has produced a higher diagnostic yield (and reproducibility) for highly genetically heterogeneous conditions compared with most other genetic test modalities, ranging from at least 25% to nearly as high as 50%[2-4] in our own center (if "likely pathogenic" variants are included among the positives). These figures are more impressive when one considers that these patients have typically gone undiagnosed for years despite standard genetic and other tests, expensive imaging, biochemical and functional studies, and visits to subspecialists.

As this diagnostic technology has already demonstrated high reproducibility and the ability to change the lives of patients for the better in other centers over the last 3 years, this study appears to be an outlier, with much smaller sample sizes.

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In Reply Whole-genome and whole-exome sequencing are already affecting clinical medicine, and we share Dr Grody and colleagues' enthusiasm in using this technology to assist disease diagnosis. Furthermore, in our study, the discovery of a *BRCA1* mutation that prompted potentially life-saving prophylactic surgery demonstrates the potential clinical effect of whole-genome sequencing in preventive medicine.

Grody and colleagues query whether the technical and interpretive challenges described in our report are related to technical problems in our laboratory, our sample population, or the use of whole-genome sequencing, and therefore outliers among recent success stories. The whole-genome sequencing for our study was performed at Illumina and Complete Genomics laboratories, so our technical experience could not reflect a peculiarity of our center.

Our results indicate not that disease gene coverage is low but rather it is incomplete in certain key areas. This finding is entirely consistent with published experience from other centers and is not unique to whole-genome sequencing or to adults without overt syndromic disease. In fact, sequencing coverage statistics from Grody and colleagues' own clinical sequencing laboratory would suggest lower coverage of key genes than we reported.[1] Of the 56 genes that the American College of Medical Genetics and Genomics recommends for incidental finding discovery and reporting, the UCLA Clinical Genomics center reports that, using whole-exome sequencing, only 29 (52%) were covered to the threshold discussed in our report (>99% of exonic bases), whereas we reported whole-genome sequencing covered 51 of 56 (91%; Illumina) to 47 of 56 (84%; Complete Genomics) genes to this threshold.