Angiotensin-Converting Enzyme Inhibitors in Black Patients

TO THE EDITOR: We read with interest the review by Brewster and colleagues (1) summarizing the effects of single antihypertensive agents on blood pressure and blood pressure control, as reported in clinical studies that enrolled black patients in both the Americas and Africa. The authors highlighted the observation that for angiotensin-converting enzyme (ACE) inhibitors, the summary effect on diastolic control (as a binary outcome) did not differ significantly from placebo. However, they also found that for these agents, changes in both systolic (−7.43 mm Hg) and diastolic (−3.35 mm Hg) blood pressure were each significantly greater than for placebo. The finding that the effect of ACE inhibition was nonsignificant in relation to placebo was based on only 3 studies, 2 of which enrolled participants with baseline diastolic blood pressure greater than or equal to 110 mm Hg. Moreover, these 2 studies apparently used per protocol analysis (as opposed to intention-to-treat analysis); when only intention-to-treat analyses were considered, the effect of ACE inhibition on control of diastolic blood pressure was significantly greater than for placebo (relative risk, 1.74 [95% CI, 1.04 to 2.92]). An additional concern is that persons who were taking multiple antihypertensive medications but had poorly controlled blood pressure were not included in these trials and were subsequently treated with a single drug regimen, a scenario that probably attenuated the in-trial response.

Distributions of blood pressure response to ACE inhibitors overlap considerably between black and white populations (2, 3). That some antihypertensive therapies have reliably distinct effects in comparable black and white populations is an unlikely premise and is also challenging because of the even greater social and genetic heterogeneity in black populations. For example, most of the genetic variability in the human species occurs within African-origin populations (4), and most genetic and social heterogeneity is within racial groups, not between them. The most sensible null hypothesis from which to work in any study of drug effects is that of homogeneity of groups, not between them. The most sensible null hypothesis from which to work in any study of drug effects is that of homogeneity across continental populations. When there is evidence of significant effect-measure heterogeneity, then this null hypothesis may be rejected and the search for biological or social explanations may commence. However, Brewster and colleagues’ meta-analysis should not be overinterpreted as providing evidence for differential treatment effects that would warrant differential prescribing patterns by race.

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IN RESPONSE: We thank Drs. Kaufman and Flack for their careful reading of our paper and for their response. They raise an important issue regarding separate consideration of hypertensive black persons when discussing treatment (1). Although there is overlap in response with other population groups, there are differences as well, and there is clearly no consensus on this matter. As a result, different national and international guidelines offer the clinician different advice on treatment of black patients.

The comments by Drs. Kaufman and Flack allow us to re-emphasize the purpose of our systematic review, which was to establish, for the first time, the efficacy of different antihypertensive drugs in hypertensive black persons through methodologically rigorous review of the existing data. The review was focused on black persons, not on comparisons with other population groups. We carefully chose this design to answer the clinical question of how best to initiate treatment in black patients, a group with greater hypertension prevalence and higher hypertension-related mortality rates (2, 3).

Authors often have very strong opinions about treatment of hypertension in black persons. Therefore, it was mandatory for us to strictly adhere to our protocol and methodologic principles, regardless of the findings. We prespecified that results would be pooled by drug type (4). Response with different baseline blood pressures was a prespecified subgroup, and sensitivity analyses included trials with per protocol versus intent-to-treat analyses. Our conclusions about the efficacy of ACE inhibitors in reaching goal blood pressure were indeed based on 3 available trials, which constituted the existing evidence. In contrast to other drugs, the effect of ACE inhibitors was not significantly different from placebo for this outcome, and this is what we highlighted. Trials that used per protocol analyses also included patients with higher blood pressures, and in these trials ACE inhibitors were particularly ineffective.

Undoubtedly, more studies are needed. As we recommended, future trials should assess the blood pressure–lowering efficacy of drugs in patients with different baseline blood pressures. Future research should also determine whether initial treatment with ACE inhibitors (as well as β-blockers and angiotensin-receptor blockers) is indeed less effective than other treatment strategies in reducing cardiovascular events, such as stroke, in black patients. Until further evidence emerges, the existing evidence we presented could guide clinicians in choosing drugs that will ensure tight blood pressure control in black hypertensive patients.

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Letters

Computed Tomography versus Endoscopic Ultrasonography for Staging of Pancreatic Cancer

TO THE EDITOR: We congratulate DeWitt and colleagues on their article comparing endoscopic ultrasonography and multidetector computed tomography (CT) for detection and staging of pancreatic cancer (1). However, we would like to highlight an inaccuracy and indicate limitations that should temper acceptance of their conclusions into current patient care.

The authors incorrectly stated that the University of Michigan study (2) comparing endoscopic ultrasonography with helical CT included patients with distant metastatic disease. Mertz and associates (3) did include 9 patients with metastatic disease in their study.

Our concerns relate to the authors’ primary outcome: detection of unresectability. Tumors were deemed unresectable by distant metastatic disease or invasion of mesenteric vessels. Distant metastases are best detected with CT, while both CT and endoscopic ultrasonography are useful for defining vascular invasion. This biases the analysis in favor of CT.

The Michigan study (2) specifically focused on vascular invasion. DeWitt and colleagues reported sensitivity for detecting T4 disease (88% for endoscopic ultrasonography vs. 71% for CT). Presumably most patients with T4 disease had vascular invasion, but this is not specifically stated. Furthermore, it seems likely that at least 9 patients (6 with liver metastases and 3 with distant nodal metastases detected intraoperatively) did not have complete dissection. This weakens the analysis regarding the ability of the tests to detect vascular invasion.

The protocol of performing endoscopic ultrasonography with fine-needle aspiration in all patients before CT is atypical. It leads to the unnecessary use of endoscopic ultrasonography in patients with distant disease and may cause inflammatory changes in the pancreas, confounding CT staging accuracy.

Most important is the problem of overstaging. DeWitt and colleagues reported that endoscopic ultrasonography and helical CT predictions of T4 disease were incorrect in 17% and 14% of cases, respectively. This indicates that patients with resectable disease would be denied potentially curative resection. Using 2 imaging methods to deem tumors unresectable has been suggested as the optimal approach, but it is not perfect (4, 5). DeWitt and colleagues’ conclusions that CT alone should guide decision making cannot be generalized to current practice. Future studies should focus not on which single imaging method is best but rather on what combination of tests or staging algorithm optimizes clinical outcomes.

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IN RESPONSE: We thank Drs. Tierney, Kochman, and Scheiman for their interest in our article. We apologize for the incorrect reference cited.

We agree that CT and magnetic resonance imaging (MRI) are superior to endoscopic ultrasonography for detection of hepatic metastases from pancreatic cancer, since most of the right lobe of the liver cannot be seen by the latter test. Therefore, endoscopic ultrasonography clearly cannot replace other methods for staging of the liver but may supplement them. However, endoscopic ultrasonography and endoscopic ultrasonography–guided fine-needle aspiration may detect and accurately sample small metastatic liver lesions missed by other imaging methods (1). Endoscopic ultrasonography may also be superior to CT for detection of celiac node metastases (2) and small quantities of peritoneal fluid (3). Therefore, the overall superiority of CT for detecting distant metastases may bias the spectrum of disease for the study but does not bias the analysis. We do not believe that improved multidetector CT imaging of the right lobe of the liver, compared with endoscopic ultrasonography, creates a significant bias in favor of CT. Furthermore, limiting analysis of enrolled patients to those with confirmed locoregional disease diminishes clinical application of our results.

In our study, only 4 patients with pancreatic cancer who underwent surgery did not have complete assessment of vascular invasion. Although it was not stated in our paper, all patients with T4 malignant disease had invasion into vessels other than the splenic artery or splenic vein. Information concerning vascular invasion was omitted from our study principally because of space limitations and to allow us to focus on detection, staging, and resectability. We agree with Tierney and colleagues that this information is critical to determining preoperative staging and intend to publish this information separately.

All patients had either CT or MRI performed outside our institution before enrollment in the study. Furthermore, those with obvious metastatic disease were excluded. Endoscopic ultrasonography–guided fine-needle aspiration was performed before multidetector CT in our study. We believe that this practice is more the
rule than the exception among tertiary care centers such as our institution. Although the risk for acute pancreatitis following endoscopic ultrasonography–guided fine-needle aspiration is 1% to 2%, no data support the contention that this potential inflammation may alter accuracy of tumor staging by CT or MRI. In our study, most CT scans were performed the same day as endoscopic ultrasonography, potentially limiting this problem.

We agree that preoperative staging of pancreatic tumors would potentially preclude resectable tumors from proceeding to surgery. However, the protocol we employed generally used surgical resection only when one or both tests showed resectability. The more relevant question, however, is whether the use of 2 tests permits a clinically meaningful increase in resectability as compared with 1 study alone. Our study did not demonstrate this but may have been underpowered to demonstrate any difference. Despite a slightly increased positive predictive value of resectability when CT or MRI is used in combination endoscopic ultrasonography (4, 5), this strategy remains debatable, although it could reduce costs (4). The use of endoscopic ultrasonography for pancreatic tumors, however, will probably remain dependent on availability, referral patterns, and local expertise.

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The Physiologic Basis of High-Altitude Diseases

TO THE EDITOR: I read West’s review on the physiologic basis of high-altitude diseases (1) with interest. A large recent trial in the Nepalese Himalayas involving 614 western trekkers convincingly showed that *Ginkgo biloba* was not effective in the prevention of acute mountain sickness (2). Perhaps this study should have been included in West’s review. Although this field study did have some limitations, it revealed that gingko caused significantly increased headache when combined with acetazolamide compared with acetazolamide alone.

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TO THE EDITOR: In his review (1), West does not mention the important role of alveolar fluid clearance in the pathophysiology of high-altitude pulmonary edema. Clearance of alveolar fluid mediated by the sodium–potassium adenosine triphosphatase (ATPase) pump present in the apical surface of the alveolar epithelium is a well-established concept (2). If this process is weakened, it may impair clearance of alveolar fluid and predispose individuals to pulmonary edema (3). Experts in high-altitude medicine have successfully attempted interventions to manipulate this process for therapeutic benefit and have put such interventions into practice.

A randomized, double-blind, placebo-controlled study of mountaineers susceptible to high-altitude pulmonary edema (4) has shown that the β-adrenergic agonist salmeterol reduces incidence of high-altitude pulmonary edema by 50%. In animal models, β-agonists have been shown to upregulate the clearance of alveolar fluid and lessen pulmonary edema (5, 6). However, salmeterol may have the additional hemodynamic advantage of preventing high-altitude pulmonary edema. The same study showed that, in low altitude, nasal transepithelial sodium and water transport in the distal airway was more than 30% lower in persons who were susceptible to high-altitude pulmonary edema than in those who were not. These findings clearly support the idea that alveolar fluid clearance may have a pathogenic role in pulmonary edema.

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TO THE EDITOR: John B. West, an icon in the field of respiratory physiology, has written an excellent review on the physiologic basis of high-altitude disease (1). The review nicely described acute moun-
tained sickness, high-altitude cerebral edema, and high-altitude pulmonary edema. Dr. West also discussed chronic mountain sickness, subacute mountain sickness, and retinal hemorrhages, disorders that are often overlooked.

However, I do believe that some points were not adequately highlighted. First, Dr. West’s review should have included more information about focal neurologic deficits, which are important to the diagnosis of high-altitude problems and many other subclinical diseases that manifest in high altitude.

Second, Dr. West should have provided more information about the genetic basis of high-altitude illness, especially high-altitude pulmonary edema. He should also have elaborated about the involvement of vascular endothelial growth factors in high-altitude cerebral edema and high-altitude pulmonary edema (2). Do angiotensin-converting enzyme, tyrosine hydroxylase, serotonin transporter, and endothelial nitric oxide synthase genes have a role in the pathogenesis of high-altitude pulmonary edema (3)? How about the association between genetic polymorphism and high-altitude pulmonary edema?

Third, the prescription of *Gingko biloba* for prevention of high-altitude disease remains questionable. Reasons for the use of *Gingko biloba* in various diseases seem vague (for example, intellectual improvement) (4), and this vagueness has now entered the field of altitude disease remains questionable. Reasons for the use of *Gingko biloba* in various diseases seem vague (for example, intellectual improvement) (4), and this vagueness has now entered the field of medicine. The Prevention of High-Altitude Illness Trial has found that *Gingko biloba* is not only ineffective in the prevention of acute mountain sickness but also reduces the efficacy of acetazolamide for prevention of acute mountain sickness among Himalayan trekkers: the prevention of high-altitude illness trial (PHAIT). BMJ. 2004;328:797. [PMID: 15070635]

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**IN RESPONSE:** All 3 letters make useful points.

In my article, I inserted the statement “*Gingko biloba* has been suggested as a useful prophylactic agent but has not been sufficiently studied” because there are several conflicting published reports, as noted by Gertsch and colleagues (1). However, I agree with Basnyat that their randomized, double-blind, placebo-controlled study is strong evidence against the value of ginkgo for the prevention of acute mountain sickness.

I also agree with Pandit that there is compelling evidence that alveolar fluid clearance in pulmonary edema is assisted by the sodium–potassium ATPase pump, and this might well have been referred to in the review. However, in my defense, it seems likely that the initial events in the pathogenesis of high-altitude pulmonary edema are the increased pulmonary vascular pressures leading to stress failure of pulmonary capillaries, as set out in the review. It is not necessary to invoke defective alveolar fluid clearance in the initial mechanism. The convincing study showing the prophylactic effects of inhalation of the β-adrenergic agonist salmeterol on the incidence of high-altitude pulmonary edema (2) is consistent with the fact that stimulation of the sodium–potassium ATPase pump helps to remove alveolar fluid but does not prove that this is a factor in the initial pathogenesis of the condition.

Matiram Pun, who must be an exceptional third-year medical student, argues that the review should have said more about focal neurologic deficits at high altitude. Again in my defense, the review stated that “patients may have papilledema and occasionally focal neurologic signs affecting cranial nerves, or even hemiparesis.” Certainly, however, the review could have cited one of the recent articles on this subject, such as that by Basnyat and colleagues (3). Possible genetic factors involved in high-altitude illnesses are a topic of interest but so far are mainly speculative. The possible role of vascular endothelial growth factor in high-altitude pulmonary edema is the subject of a very recent article (4).

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**Correction**

Correction: Plasma Level of a Triggering Receptor Expressed on Myeloid Cells-1

The third, fourth, and fifth paragraphs in the Discussion of an article published in _Annals of Internal Medicine_ (1) contain unattributed material similar to 2 paragraphs in the Discussion of another article (2). The authors of the _Annals_ article have acknowledged their error, and the authors of the earlier article have accepted their apology. None of the text in question contains any factual errors.

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