TO THE EDITOR: The investigators of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) (April 10 issue) report that telmisartan is equivalent to ramipril in patients with vascular disease or high-risk diabetes. However, the primary composite end point of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure was not lower in the combination-therapy group than in the group receiving ramipril alone, even though blood-pressure levels in the combination-therapy group were 2.4/1.4 mm Hg lower than those in the ramipril group throughout the study period. Still more disturbing was a trend in the combination-therapy group toward even more deaths from cardiovascular and noncardiovascular causes than in the ramipril or telmisartan group (deaths from cardiovascular causes, 620 vs. 603 and 598, respectively; deaths from noncardiovascular causes, 445 vs. 411 and 391, respectively). Given that the number of patients with hyperkalemia was much higher in the combination-therapy group than in the ramipril or telmisartan group (480 vs. 283 and 287, respectively), as was the number of patients with hypotensive symptoms (406 vs. 149 and 229, respectively), we wonder whether a specific cause of death (i.e., sudden death or death from arrhythmia) can be identified in the combination-therapy group. Data from such an analysis should be provided.

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TO THE EDITOR: We are puzzled by the concluding statement of McMurray, in his editorial accompanying the report on the ONTARGET trial, that “Because ARBs [angiotensin-receptor blockers] are more costly than ACE [angiotensin-converting–enzyme] inhibitors and have more side effects, their primary value is as an alternative for patients who cannot tolerate ACE inhibitors.” The ONTARGET trial directly contradicts this statement. Although 621 patients permanently discontinued ramipril, only 438 patients permanently discontinued telmisartan. When hypotensive symptoms of an antihypertensive drug (an expected effect) are omitted, more than twice as many patients discontinued ramipril as discontinued telmisartan. Also, so-called hypotensive symptoms have little meaningful value unless the corresponding blood pressure is recorded. In addition, several randomized trials have shown that ARBs have fewer adverse effects than ACE inhibitors (Table 1). Notably, in ONTARGET, angioedema, which can be fatal, was 2.5 times as common in patients receiving ramipril as in those receiving telmisartan. These findings clearly do not attest to the conclusion that ARBs have a greater number of adverse effects than ramipril, as stated by McMurray.

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Dr. Messerli reports serving on speakers’ bureaus for Abbott, GlaxoSmithKline, Novartis, Pfizer, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Forest, Sankyo, and Sanofi-Aventis and receiving research grants from GlaxoSmithKline, Pfizer, Novartis, and CV Therapeutics. Dr. Ram reports serving on speakers’ bureaus for Advanced Health Media, COGENIX, and GENESIS, which conduct educational programs for companies that manufacture pharmaceuticals and medical devices. No other potential conflict of interest relevant to this letter was reported.

4. Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with sympto-


The editorialist replies:
I referred to the only two trials that showed noninferiority of an ARB as compared with an ACE inhibitor and therefore permit a legitimate comparison of tolerability.1 In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), valsartan led to significantly more reductions in the dose of the study drug because of hypotension and renal dysfunction than did captopril. Treatment discontinuation because of hypotension was also significantly more common with valsartan (and discontinuation due to renal dysfunction was numerically more frequent with valsartan). As expected, cough was much less common with valsartan.

Only study-drug discontinuations were reported (as multiple episodes) in ONTARGET, but exactly the same pattern was observed. It is important to note that the net difference of 137 more discontinuations for any reason with ramipril reflected the balance of 267 fewer discontinuations because of cough with telmisartan, offset by other adverse effects that in my opinion may be more clinically significant (e.g., hypotension, for which there was a net excess of 80 cases with telmisartan).

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Anesthesia Awareness and the Bispectral Index

TO THE EDITOR: Avidan et al. (March 13 issue)4 confirm that bispectral index (BIS)–guided care achieves a 0.2% incidence of awareness during anesthesia in high-risk patients, as previously reported,3 but further conclusions and recommendations are not supported. Despite the investigators’ original hypothesis “that the incidence of awareness [with an end-tidal protocol] will be equivalent to or lower” than that with a BIS-guided protocol,3 the sample-size calculation erroneously assumed no treatment effect for the anesthetic protocol (Table 1). Consequently, this study had an 80% probability of missing a 50% difference in the relative efficacy of the two interventions.4

Unexplained gaps in BIS trends suggest that inadequate training or vigilance and poor proto-