ade (2) and a fall in HR (1). Thus, a low HR would be linked to a high central pressure.

In contrast, second-line beta-blockade alongside a first-line agent that improves vascular compliance and lowers central pressures in the elderly (e.g., a low-dose diuretic or calcium antagonist [4]), is linked to highly significant falls in CV end points as in the SHEP (Systolic Hypertension in the Elderly Program), ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), and MRC (Medical Research Council)-Elderly (2) studies.

The next 2 main contributor trials (1) were the IPPPSH (International Prospective Primary Prevention Study in Hypertension) and HAPPHY (Heart Attack Primary Prevention in Hypertension) trials involving young/middle-aged hypertensive patients. The first-line beta-blockers were nonselective oxprenolol and partially beta-1 selective atenolol/metoprolol—beta-blockers that lower blood pressure in different ways (5). Metoprolol and atenolol act via a fall in HR and cardiac output; oxprenolol acts via a modest fall in HR and cardiac output plus a modest fall in peripheral resistance via beta-2 intrinsic sympathomimetic activity. Thus, linking a final HR or HR difference with CV events is unhelpful. For atenolol/metoprolol, quoting intra-trial (rather that end-trial) changes in HR (if known) would be useful, enabling HR/CV-event relationships to be studied.

Cigarette smoking is another relevant, vital issue for younger and middle-aged hypertensive patients, as significant benefit with oxprenolol (IPPPSH), propranolol (MRC-1), and metoprolol (MAPHY [Metoprolol Atherosclerosis Prevention in Hypertensives]) occurred only in nonsmokers (2). Nonsmokers (70% of the whole) in MRC-1 experienced a significant 38% reduction in CV events on propranolol, similar to the results of atenolol versus less-tight blood pressure control in overweight middle-aged hypertensive patients with type-2 diabetes in the UKPDS (United Kingdom Prospective Diabetes Study) (6,7), in which all 7 hard end point trends (including myocardial infarction and stroke) favoring the beta-blockers over the angiotensin-converting enzyme inhibitor at 9-year follow-up (7), strengthened over 20-year follow-up, achieving significance in the case of all-cause death (8). Smoking induces epinephrine release (9) and in the presence of beta-1/beta-2 blockade, unopposed alpha stimulation occurs; the resultant increase in blood pressure induces reflex falls in HR (10). In such a scenario, a low HR would be linked to an increase in CV events. Such a worrisome beta-blocker-epinephrine interaction is not observed with high beta-1 selectivity (e.g., bisoprolol) (11).

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Reply

We thank the several authors who wrote a letter concerning our recent paper (1).

1. Dr. Phillips's criticism of our observation, being possibly the result of confounding by indication, needs to be considered carefully. Although we do not have definitive evidence to rule this out, we think it is unlikely because in our data, there was poor correlation between heart rate achieved at the end of treatment and the systolic blood pressure difference between the treatment modalities ($r = 0.154$; $p = 0.717$). Similarly, there was no correlation between heart rate achieved and diastolic blood pressure difference between treatment modalities ($r = -0.255$; $p = 0.542$). This would indicate that the negative chronotropic effect of beta-blockade can, to some extent, be dissociated from its antihypertensive effect. However, as Dr. Phillips indicates, the only way to rule out confounding by indication would be in looking at the individual patient data, which obviously is no longer possible.
2. We agree with Drs. Aursnes and Osnes as well as with Dr. Cockcroft that most of the findings in all meta-analyses of beta-blocker trials are driven by atenolol. However, atenolol remains the most widely prescribed beta-blocker worldwide, with more than 40 million prescriptions per year in the U.S. alone. No head-to-head comparisons of atenolol with other beta-blockers have been done. Until we have convincing morbidity and mortality data in trials done with beta-blockers other than atenolol, we should not automatically exculpate these agents. Thus, it is high time to sound the death knell for atenolol, as Dr. Cockcroft suggests, but we should continue prescribing beta-blockers (particularly those with a better hemodynamic and metabolic profile) for well-defined cardiovascular indications.
3. We take issue with Dr. Gupta's statement that our study merely seeks "to convert a small-to-moderate statistical relative risk into an absolute biological risk with important practical impli-

cations." The inefficacy of beta-blockers to prevent heart attack and stroke in hypertension patients has been extensively documented and, at least for atenolol, is beyond any doubt. Dr. Gupta's point that beta-blockers specifically may prevent headaches, which are common in hypertension, has not been substantiated by data. Headaches have been clearly shown to be less common with all antihypertensive therapy (regardless of class) than with placebo (2).

4. Drs. Laurent and Boutouyrie's reanalysis of data from our meta-analysis indicates that heart rate at baseline (before antihypertensive therapy) may have acted as a confounding factor in our analysis. We obviously cannot rule this possibility out, but we would like to point out that a subanalysis of the CAFE (Conduit Artery Function Evaluation) study extended and corroborated our findings (3). Moreover, analyses of our data done with cardiovascular outcomes as a function of the mean heart rate reduction (baseline minus end of treatment) with beta-blockers also showed similar relationships, that is, the greater the reduction of heart rate was with beta-blockers, the higher the risk was of cardiovascular events.
5. The point of Dr. Khan, that beta-blockers are less effective at preventing cardiovascular events than other antihypertensive agents, is correct. We do not think that beta-blockers actually increase cardiovascular events. However, despite a fall in blood pressure, they do not decrease cardiovascular events in hypertensive patients, thereby providing a false sense of security to patients and physicians: blood pressure is controlled, yet risks of heart attack and stroke remain unchanged. Pooled analyses report that beta-blockers reduce the risk of stroke by 16% to 22% when compared with placebo. However, this risk reduction is suboptimal compared with the 38% reduction for the same degree of blood pressure reduction observed with the use of other antihypertensive agents (4).
6. We agree with Dr. Fragasso and colleagues that not all beta-blockers are created equal. Some of the newer agents such as nebivolol and carvedilol are metabolically and hemodynamically more patient friendly than the traditional agents and do not impair endothelial function. However, outcomes data with newer beta-blockers in hypertension are lacking, so it remains uncertain whether these benefits of surrogate end points will result in benefits of morbidity and mortality.
7. Dr. Cruikshank has an established track record of aggressively defending beta-blockers. He is correct though in that the MRC (Medical Research Council) study showed some benefits of propranolol in average 47-year-old male British smokers. This finding was the result of much data dredging; in the main study there was no difference in all-cause mortality, heart attack, and stroke between propranolol and placebo. In the same MRC studies, twice as many patients dropped out because of adverse events on beta-blockers than on diuretics. In fact, these studies allow us to calculate that for every heart attack or stroke prevented, 3 patients were made impotent by beta-blockers and 8 experienced fatigue to the extent that they withdrew from the study (5). This seems hardly an acceptable risk-to-benefit ratio for patients with a completely asymptomatic disease such as stage I essential hypertension.

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