partly due to the secondary effect of being thin, and not the direct result of the CR diet.

Finally, the small number of adherents to a CR life-style speaks to the difficulty in depriving oneself every day of preferred type and amounts of food. We hypothesize (5) that alternate-day calorie restriction, in which one eats less and more than needed to maintain body weight on alternating days, will provide the same health benefits as daily CR; it is a much more agreeable way of living, and it appears to have a profound effect on cardiac function (6).

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REPLY

We appreciate the views expressed by Dr. Johnson and colleagues regarding our recent study (1) concerning caloric restriction (CR) and diastolic function (DF). We agree that in large population studies, diastolic dysfunction, body mass index (BMI), and adiposity are correlated. It would be ideal to have a BMI and body-fat–matched control group that is healthy and not calorie restricted. Individuals with a BMI >20 kg/m² who are not calorie restricted. Individuals with a BMI <20 kg/m² who are not CR restricted are generally in ill-health and frail or heavy smokers. Endurance exercise training causes major cardiovascular adaptations, so athletes are also not an appropriate control group. The control group in our study consisted of individuals typical of the U.S. population, as 78.2% of the men and 68.1% of the women older than 40 years are overweight or obese in the U.S. (2).

In our study (1) we provided evidence that, in humans, long-term CR with optimal nutrition (at least 100% of the recommended daily intake for each nutrient) results in very low levels of inflammation, as demonstrated by low serum C-reactive protein and tumor necrosis factor-alpha concentration, and reduced left ventricular stiffness, indicated by the lower model-based image processing–derived chamber stiffness parameter £ and viscoelastic chamber constant c. We also found that CR is associated with low serum concentrations of transforming growth factor-beta, a powerful pro-fibrotic molecule that plays a role in regulating the myocardial composition of the extracellular matrix, thus potentially having salutary effects on £ and c (3).

In contrast, individuals who are very thin owing to chronic diseases generally have elevated levels of systemic inflammation and have diastolic dysfunction despite a low BMI (4–6). For the group considered, long-term CR is the cause, and the coexistent low BMI is one effect. Conversely, we are not aware of any mechanism by which a low BMI, as an independent variable, can improve DF. The improved DF observed is mediated by other CR effects, such as lowering blood pressure and decreasing the levels of inflammatory cytokines, hormones, and growth factors that may reduce fibrosis, increase compliance, and improve cardiac efficiency.

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Implications and Controversies of Recent Hypertension Trials

Williams has written a comprehensive and thought-provoking review of the recent hypertension literature (1). One of his major contentions is an iteration of the hypothesis that achieving better cardiovascular outcomes depends on more aggressive blood pressure (BP) control and not on the specific choice of antihypertensive
agents. In particular, the claim is made that the benefits of ramipril and perindopril evidenced in the HOPE (Heart Outcomes Prevention Evaluation) (2), and EUROPA (EUropean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease) (3) trials, respectively, are due to the lower BP levels achieved by these agents in the treated groups. However, when a similarly decreased level of BP is achieved in thetrandolapril-treated group in the PEACE (Prevention of Events with Angiotensin Converting Enzyme inhibition) (4) trial, no cardiovascular outcomes benefit is observed.

Does not this dichotomy denigrate the concept that only the achieved BP level is what matters? Do the results of these three trials suggest that perhaps differences exist among angiotensin-converting enzyme inhibitors beyond their additive BP effects?

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**REPLY**

In a previous review, I stated that the data from large-scale clinical trials of the treatment of hypertension suggested that the main driver of benefit from blood-pressure (BP) lowering drugs was the BP lowering per se (1). Dr. Schwartz in his response to this review notes that, although the HOPE (Heart Outcomes Prevention Evaluation) (2) and EUROPA (EUropean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease) (3) studies showed benefits of angiotensin-converting enzyme (ACE) inhibition versus placebo in reducing cardiovascular events in patients with cardiovascular disease, the more recent PEACE (Prevention of Events with Angiotensin Converting Enzyme inhibition) (4) study did not. Dr. Schwartz states that this dichotomy might suggest within-drug-class differences, pointing to the benefit of specific ACE inhibitors “beyond blood pressure.” This concept is tenuous at best and could only be proven by testing different ACE inhibitors head-to-head in the same patient population.

The differences in outcomes when comparing the HOPE and EUROPA trials with the PEACE trial reflect different patient populations and differences in concomitant medications. Compared to the HOPE and EUROPA trials, the the PEACE trial cohort was more aggressively treated with lipid-lowering drugs (70%), antiplatelet drugs (90%), and beta-blockers (60%), and in such an aggressively treated population it was not even possible to show an additional benefit of the ACE inhibitor-induced BP lowering. The message from the PEACE study was admirably summed up by the investigators: “in a population of patients with coronary artery disease and preserved ejection fraction who receive intensive current standard therapy..., there appears to be no evidence of cardiovascular benefit from the addition of ACE-inhibitor therapy” (4).

With regard to treating hypertension in an endeavor to prevent the development of fatal or nonfatal myocardial infarction (MI), the ALLHAT (Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial) study tested this hypothesis and failed to show an advantage of ACE inhibition (5). Moreover, the more recent CAMELOT (Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis) study also failed to show an advantage of ACE inhibition over the comparator, a calcium channel blocker (CCB) in patients with angiographically proven coronary disease (6). Finally, meta-analyses of hypertension trials have consistently failed to show an advantage of ACE inhibitor-based therapy over other classes of BP lowering therapy in the prevention of MI (1).

I concede that on the basis of our recent data from the CAFE (Conduit Artery Function Evaluation) study, it is possible to go beyond brachial BP, depending on the choice of the BP-lowering agent (7). In the CAFE study we showed that beta-blocker + thiazide-based therapy was less effective at lowering central aortic pressure when compared to a CCB + ACE inhibitor-based treatment, despite similar effects on brachial BPs. Thus, it is plausible that brachial BP measurements underestimated the beneficial effects of ACE inhibition on central aortic BPs in the HOPE and EUROPA trials. However, even then it is still pressure and hemodynamics and not mysterious biology that explain the benefit of the drugs in these trials.

It is surely beyond dispute that the most effective way to “go beyond blood pressure” to prevent MI in patients with hypertension at high risk of cardiovascular disease is to add a statin to their therapy (1). No amount of ACE inhibition will compete with this, no matter what clothes the emperor wears—indeed, on the basis of evidence alone, with regard to ACE inhibition and the prevention of MI by drug-specific effects, the emperor has no clothes!

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