

CORRESPONDENCE

Letters to the Editor

Blood Pressure Levels on Progression of Coronary Atherosclerosis

The provocative study by Sipahi et al. (1) looking at progressions of coronary artery disease (CAD) in hypertension by intravascular ultrasound (IVUS) and the accompanying editorial by Tobis and Fonarow (2) do not quite clearly distinguish between the effects of blood pressure (BP) lowering on prevention or progression of CAD and the effects of BP lowering as a treatment modality in patients with manifest CAD. There is little surprise that the lower the BP, the better CAD will be prevented or its progression reversed. Numerous clinical and experimental low BP models are characterized by little, if any, atheromatosis in the exposed vascular bed. In fact, to put it pointedly, a zero BP would probably eliminate CAD completely. However, in patients with established CAD, several studies have shown that lowering diastolic pressure below certain levels will increase the risk of acute coronary events.

Based on our recent findings of a subanalysis of the 22,000-patient INVEST (International Verapamil-Trandolapril Study) (3), we would like to caution about too aggressive BP lowering in hypertensive patients with CAD. This holds particularly true for diastolic pressure and less so for systolic pressure. In the INVEST study (3), the nadir for primary outcome (all-cause death and total myocardial infarction) was J-shaped, with a nadir at 119/84 mm Hg (3). When diastolic pressure dropped below 70 mm Hg the adjusted hazard ratio of primary outcome doubled, and below 60 mm Hg it quadrupled. Because the coronary arteries are perfused during diastole only, coronary perfusion may become hampered when diastolic pressure falls excessively in patients at risk (i.e., those with CAD). Of note, in the study by Sipahi et al. (1) only systolic but not diastolic pressure was a significant determinant of progression of CAD. Thus, their concluding statement that “the most favorable rate of progression of coronary atherosclerosis is observed in patients whose BP falls within the “normal” Joint National Commission-7 category (i.e., systolic BP <120 mm Hg and diastolic BP <80 mm Hg)” and that “the optimal BP goal may be substantially lower than the <140/90 mm Hg” should be amended by refraining from identifying any levels of diastolic pressure.

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Reply

Regarding our study (1), Dr. Messerli et al. state that, in patients with coronary disease, lowering diastolic blood pressure (BP) below certain levels will increase risk of acute coronary events, and they urge us to amend our conclusion, stating “the most favorable rate of progression of coronary atherosclerosis is observed in patients whose BP falls within the ‘normal’ Joint National Commission-7 category (i.e., systolic BP <120 mm Hg and diastolic BP <80 mm Hg).” They base their argument on the secondary analysis of the INVEST (International Verapamil-Trandolapril Study), which suggested a J-shaped relationship between diastolic BP and the primary outcome that included not only all-cause death and nonfatal myocardial infarction (MI), as stated in the above letter, but also nonfatal stroke (2).

However, in the INVEST study there were profound imbalances in the baseline characteristics of patients with lower and higher diastolic BP. For example, as compared to patients with a diastolic BP of 70 to 80 mm Hg, patients with diastolic BP <60 mm Hg were older (74 vs. 67 years), more likely to have a history of MI (47% vs. 32%), bypass surgery and angioplasty (48% vs. 28%), and diabetes (44% vs. 29%). More importantly, they were about 4 times more likely to have heart failure (22% vs. 5%) and cancer (11% vs. 3%). Indeed, when adjusted for these confounders, the J-shaped relationship between diastolic BP and the primary outcome disappeared. This shows that the increased primary outcome with lower diastolic BP levels was due to the fact that these patients were sicker beforehand (i.e., reverse causality). In fact, analysis of MRFIT (Multiple Risk Factor Intervention Trial) data involving more than 300,000 men with a median follow-up of 22 years showed that, within the normal BP category of <120/80 mm Hg, there exists no relationship between diastolic BP and cardiovascular disease mortality (3). Our conclusion about the importance of having normal BP levels to slow progression or induce regression of coronary atherosclerosis as assessed by intravascular ultrasound is also supported by other epidemiological data including the Framingham study, which showed that incidence of MI is lowest in patients with normal BP, intermediate in those with prehypertension, and highest in those with hypertension (4).

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Is Homocysteine a Risk Factor for Atherothrombotic Cardiovascular Disease?

In a recent state-of-the-art study, Kaul et al. (1) have not validated the hypothesis of homocysteine as a risk factor for atherothrombotic cardiovascular disease. These conclusions will have major implications for the developing countries that derive cutting-edge knowledge of cardiovascular disease from the West (2).

There is consistency in the mean homocysteine level in patients with coronary artery disease (CAD) from Pakistan and India of about 19 $\mu\text{mol/l}$ (3–8). This finding is significant because the South Asian population has the highest known rate of CAD, which is widespread, early onset, and is aggressive (9). They have higher propensity for clinical events compared with other populations even after adjusting for all known risk factors and the degree of atherosclerosis (10).

The concept of homocysteine being a proximate risk factor with short incubation period and its strong interaction with conventional risk factors provides a biological plausibility that, in South Asians, homocysteine owing to its prothrombotic effects and interaction with conventional risk factors may increase the propensity of this population to develop coronary atherothrombotic disease (11). According to one estimate, in Pakistan nearly 100,000 individuals suffered from acute myocardial infarction in calendar year 2002 (12). These observations are undermined especially in meta-analyses as a majority of the studies are done in the population with lower mean homocysteine values. The sample size in the meta-analysis of patients with homocysteine $>15 \mu\text{mol/l}$ and especially in the range of 19 $\mu\text{mol/l}$ is not powered to give statistically significant conclusions. This observation is obvious in

the high-impact trials like HOPE (Heart Outcome Prevention Evaluation)-2 and NORVIT (Norwegian Vitamin Trial), where the mean homocysteine values of patients were 12.2 $\mu\text{mol/l}$ and 13.0 $\mu\text{mol/l}$, respectively (13,14). In view of the mandated fortification of food products in the U.S., it was predicted beforehand that the statistical power of the ongoing trials would be marked by power shortage (15).

Ironically, the trend-setting study “Folate Therapy and In-Stent Restenosis After Coronary Stenting” (16) in its conclusion never mentioned the trend toward the beneficial effect of folate replacement in patients with homocysteine levels $>15 \mu\text{mol/l}$, and the study became a landmark trial showing increase risk of in-stent restenosis with folate therapy, which was documented in patients with homocysteine levels $<15 \mu\text{mol/l}$.

The scenario is further biased by the fact that after folic acid fortification in the United States, a population-wide reduction in blood homocysteine concentration has been seen; according to one estimate, the proportion of patients with homocysteine $>15 \mu\text{mol/l}$ decreased from 41% to 28%. This mean decrease in homocysteine levels in this population has nicely translated in terms of trend toward mortality benefit in cardiovascular disease and definite improvement in stroke-related mortality (17,18). These facts are well appreciated by Kaul et al. in defining the therapeutic range of high-risk individuals in the recommendations for screening and treatment of elevated homocysteine levels.

How do developing countries, which form a major chunk of global burden (2) of cardiovascular disease, reconcile with the invalidation of homocysteine hypothesis for atherothrombosis? In the long run, its repercussions could be in the form of the 10/90 gap, which refers to the global situation where only 10% of billions of dollars is devoted to health research, which accounts for 90% of total health burden (19).

Finally, this state-of-the-art study is food for thought in context to the philosophy to achieve maximum diversity nicely highlighted by Anthony DeMaria in the *Journal's* Editor's Page, “Diversity in *JACC*” (20).

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