

trial (9). In HPS, no significant differences were found in cognitive function or diagnosis of dementia between treatment groups during this 5-year study with simvastatin. The PROSPER study also specifically and prospectively addressed cognitive function, including dementia, in its study population of patients aged 70 to 82 years (average 75 years) who demonstrated no evidence of cognitive dysfunction at study entry, and found no effect of pravastatin treatment on this domain during a 3-year trial (10). Based on these two large-scale prospectively designed investigations, we can conclude that statin therapy does not appear to have any beneficial or adverse effect on cognitive function assessed over a 3 to 5-year period. Conceivably, a longer follow-up time may be needed to detect a significant impact on dementia (11).

Most recently, because of the considerable attention given to this topic by the lay media, many patients have been concerned about statins actually causing memory loss and cognitive impairment. Although this idea is mostly based on isolated case reports without causality being established (12,13), the media attention given to this topic has led to numerous phone calls to physicians' offices as well as some patients stopping their statins. Although these reports raise the possibility that statins, in rare cases, may be associated with cognitive impairment, this is not supported by data in over 30,000 patients in the two large-scale prospective studies (9,10).

Further studies are needed before routinely adjusting therapeutic targets for LDL in patients without ACS especially to targeted LDL levels between 50 to 70 mg/dl, and long-term studies are still required to better assess the clinical impact of statins on cognitive function.

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REPLY

Since our study appeared in *JACC* (1), an update to the National Cholesterol Education Program (NCEP) ATP III Guidelines drafted by a panel of lipid experts (2) concurred that lower is in fact better, and called for aggressively reducing low-density lipoprotein (LDL) cholesterol to <70 mg/dl in high-risk patients. We disagree with Drs. Lavie and Milani that this more aggressive LDL target should be applied only to patients recovering from an acute coronary syndrome. A consistent body of evidence shows a close relationship between on-treatment LDL (extending to 70 mg/dl and below) and risk of cardiovascular events in both primary and secondary prevention. Another large, randomized, placebo-controlled trial, the Collaborative Atorvastatin Diabetes Study (CARDS), has been presented since our study was published (3). This trial randomized 2,838 patients with type-2 diabetes, but with no documented atherosclerotic vascular disease, to either atorvastatin 10 mg or placebo. Atorvastatin lowered the LDL cholesterol, which was only 119 mg/dl before treatment, to 73 mg/dl. The CARDS trial was halted early owing to a 37% reduction in major cardiovascular events in the atorvastatin group.

We would agree that the benefits of statins in reducing the incidence of Alzheimer's disease is more speculative at the present time. Dementia is usually a heterogeneous disorder representing a mixture between the neurodegenerative disease processes and microvascular and large-vessel disease related to atherosclerosis and endothelial dysfunction. Virtually all of the risk factors for Alzheimer's disease (e.g., hypertension, insulin resistance, diabetes, smoking, hypercholesterolemia, and age) are also risks for atherosclerosis and microangiopathy (4). Trial data clearly demonstrate treatment of hypertension reduces the incidence of dementia. Case-control studies consistently show an association between statin use and reduced incidence of Alzheimer's disease (3). Although the PROSPER trial did not show benefit for pravastatin in reducing dementia in elderly patients, the trial lasted only 3 years, and the reduction in LDL was modest. Long-term randomized trials using potent statins to achieve and maintain LDL cholesterol under 70 mg/dl will be required to definitively answer the question regarding the ability of statins to prevent Alzheimer's disease.

Conversely, the ability of statins to reduce stroke risk is well documented. The CARDS trial found atorvastatin reduced the incidence of stroke in diabetic patients by 48% (3). A recent meta-analysis of randomized controlled statin trials showed that for every 5 years of treatment, the relative risk of stroke decreases proportionately to LDL reduction, with atorvastatin reducing stroke by 41% over 5 years, simvastatin up to 34%, and pravastatin

by 31% (5). Because stroke is a major cause of dementia, statins must be considered potentially valuable agents for preventing cognitive decline in patients with risk factors for atherosclerosis or dementia.

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Does Inhaled Nitric Oxide Support the Hemodynamic of Spontaneous Breathing Patients With Cardiogenic Shock Related to Right Ventricular Myocardial Infarction?

We read with great interest the echocardiographic study published by Inglessis et al. (1) concerning hemodynamic effects of inhaled nitric oxide (NO) in right ventricular myocardial infarction (RVMI) and cardiogenic shock (CS). They found that inhaled NO results in acute hemodynamic improvement when administered to patients with RVMI and CS.

We have a major concern with these results. Indeed, although 10 of 13 patients were under positive pressure ventilation, the investigators leave the reader with the feeling that inhaled NO results in significant hemodynamic improvement and a reduction of right to left shunting when administered to all types of patients.

In our opinion, we may expect that the observed NO effect could not be shown in spontaneous breathing patients. Indeed, as stated by the researchers, breathing NO is thought to increase pulmonary venous return and left ventricular filling pressure when cardiac output is decreased (2). Because positive pressure ventilation acts as a circulatory pump (3) and decreases left ventricular transmural pressure, acute left ventricular failure may occur when the lungs are not mechanically assisted.

In this setting, we suggest to Inglessis et al. (1) not to extend their conclusions regarding the hemodynamic inhaled NO effects to spontaneous ventilated patients with acute RVMI and CS.

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REPLY

We thank Dr. Bendjelid for his interest in our work (1). We agree that the majority of our patients were studied while undergoing positive pressure ventilation. As only three patients in our study population did not require mechanical ventilation, our ability to extrapolate our results to patients with right ventricular myocardial infarction (RVMI) not receiving mechanical ventilation is limited. Nonetheless, there was no difference in the improvement in cardiac index observed between those patients breathing nitric oxide (NO) who were mechanically ventilated and those who were not.

Dr. Bendjelid also raises the concern that positive pressure ventilation may act to prevent the development of acute left ventricular (LV) failure that may occur during NO inhalation, and that LV failure may arise in nonventilated patients. Left ventricular filling pressures have been found to increase during NO inhalation in patients with severe LV systolic dysfunction (2,3). The RVMI patients in our study had primarily RV dysfunction, and the degree of LV dysfunction was not as severe as in those patients in whom the pulmonary capillary wedge pressure (PCWP) has been reported to increase during NO inhalation. Furthermore, we excluded patients with a PCWP >25 mm Hg from study. In the three nonventilated RVMI patients in our study, we did not observe an increase in their PCWP while they were breathing NO for 10 min.

In future studies of the effects of sustained NO inhalation in RVMI patients, it will be important to observe the hemodynamic effects of this agent in patients who receive positive pressure ventilation as well as those who do not. Patients with severe LV systolic function should be monitored carefully during chronic NO inhalation because of the possibility of their developing pulmonary venous hypertension.