rate at baseline and was completely ineffective in those with low heart rate. Although it remains unclear whether beta-blocker therapy in coronary patients should be targeted according to pre-treatment heart rates, it is important to note that heart rate is also largely affected by lifestyle-related factors.

The decreased heart rate of endurance athletes is well known, and in recent studies on coronary patients, exercise therapy that led to meaningful, clinically beneficial effects was associated with significant heart rate reduction. In addition, high intake of docosahexaenoic n-3 fatty acid, an essential feature of the Mediterranean diet, is associated with decreased heart rate. Finally, sympathetic dominance with higher heart rates may be enhanced by anxiety and depression. Elicitation of the relaxation response and meditation have been shown to decrease adrenergic receptor sensitivity and to increase parasympathetic activity, thereby leading to reduction of heart rate.

Therefore, in the clinical approaches to reduce heart rate in coronary patients, effective non-pharmacological options should also be considered. Further studies may also clarify whether non-pharmacological heart rate reduction may have a comparable protective efficacy as that of beta-blocking agents in primary and secondary prevention of myocardial infarction.

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Heart rate reduction through lifestyle modification: reply

We thank Drs Michalsen and Dobos for their comments. Resting heart rate is indeed a strong predictor of mortality in patients with coronary artery disease. Experimental data have demonstrated that a reduction in heart rate can delay the progression of atherosclerosis in animal models. Atherosclerosis progression has also been shown to be predicted independently by minimum heart rate in men after myocardial infarction. Coronary artery endothelial cell dysfunction associated with high heart rates may represent an important mechanism for increased atherogenesis. In addition, a mean heart rate > 80 b.p.m. has also been shown to be associated with a higher risk of atherosclerotic plaque disruption.

Drs Michalsen and Dobos are correct in pointing out that the decrease in cardiovascular events after myocardial infarction. We entirely agree that non-pharmacological options to heart rate reduction should be evaluated and compared with pharmacological approaches. However, it is unfortunately often difficult to obtain significant lifestyle changes (such as exercise and diet) in large number of patients in the clinical setting. Because beta-blockers may have other actions including the unmasking of alpha-adrenergic-mediated coronary vasoconstriction and deleterious changes in lipid and glucose metabolism, it may also be very interesting to evaluate the effects of a pure heart rate-reducing agent that selectively acts on the sino-atrial node such as the I$_1$ channel inhibitor ivabradine. The clinical efficacy of directly targeting heart rate reduction to decrease morbidity and mortality needs to be determined in patients with coronary artery disease.