Does lipid-lowering medication improve cardiac sympathetic nerve integrity?

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As evidenced by the prospective “*AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF)*” trial, the catecholamine analogue radiotracer 123I-metaiodobenzylguanidine (123I-mIBG) holds the potential for risk stratification among high-risk individuals with severely impaired cardiac function.¹ Its prognostic performance is based on semi-quantitative analysis, e.g. by calculating a heart-to-mediastinum ratio (HMR) on 4-hour delayed planar images, whereby patients below a certain threshold are at increased risk to experience any cardiac event. As a complementary measure, increased myocardial washout rate, which also considers background subtraction, is also associated with a worse outcome.¹ Notably, the concept of assessing cardiac nerve integrity by 123I-mIBG scintigraphy to identify high-risk congestive heart failure (CHF) patients has been further expanded by *Nakajima* and coworkers.² Integrating the amount of denervated myocardium by 123I-mIBG scans and clinical parameters, dedicated 2- and 5-year mortality risk estimations charts could be provided, which allow for a more flexible short- and long-term management.² In patients with acute myocardial infarction (MI), a simultaneous assessment of cardiac innervation and perfusion/viability has established that regional

sympathetic neuronal damage exceeds the area of hypoperfused tissue.³ Thus, sympathetic neurons appear to be more susceptible to ischemic injury than cardiomyocytes, which may help in identifying (pro-)arrhythmic, denervated but viable areas-at-risk, such as the infarct borderzone.^{4,5} Given its incremental value in outcome prediction, studies in recent years have also investigated the complementary benefit of cardioprotective medication on the cardiac sympathetic nervous system (SNS) in combination with the overall ventricular performance among CHF patients.^{6–8}

The prescription of statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) is endorsed by current guidelines of the American College of Cardiology and American Heart Association.⁹ In patients with history of MI, high-intensity statins should be initiated which leads to significant reduction of cardiac events for primary and secondary prevention.⁹ As such, a recently published meta-analysis of the *Cholesterol Treatment Trialists’ (CTT) Collaboration*, enrolling 170,000 participants in 26 randomized trials, reported that a reduction of the low-density lipoprotein (LDL) cholesterol by 2–3 mmol/L lowers the risk of heart attack, revascularization or ischemic stroke by approximately 40–50 %.¹⁰ In addition, an extensive body of evidence supports the modulatory effect of statin therapy on the cardiac SNS and attenuation of left ventricular remodeling,^{11,12} predominantly driven by inhibition of central angiotensin II signaling and the superoxide pathway.¹³ In the present issue of the *Journal of Nuclear Cardiology*, *Takahashi* and coworkers investigated the impact of statins on cardiac nerve integrity derived by 123I-mIBG scintigraphy. A propensity-matched analysis was conducted to correct for selection bias, and 30 individuals with ST-segment elevation MI (STEMI) treated with statin therapy were compared to 30 MI patients without statin therapy. Following coronary angioplasty, clinical characteristics such as age, gender or recanalization times were comparable between both groups. However, in cardiac 123I-mIBG scans

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conducted 3 weeks after MI, the statin group showed significantly higher delayed HMR (along with a reduced washout rate), reflecting improved cardiac nerve integrity, compared to the non-statin group. While not significant, this improvement in cardiac nerve integrity in the statin group was paralleled by a slight increase of LVEF derived by echocardiography performed at baseline and 3 weeks later. In addition, the plasma procollagen type III amino terminal peptide (PIIINP) was investigated, which serves as a biomarker for myocardial fibrosis in patients suffering from CHF. Notably, the delta of PIIINP (derived by blood values at baseline and 3 weeks after treatment) was lower in the statin group, which is also associated with a better outcome.¹⁴ The authors concluded that statin therapy improves cardiac nerve function in patients with recent STEMI, which in turn may attenuate ventricular remodeling and cardiac fibrosis.

Takahashi and colleagues shed light on the potential modulatory effect on cardiac nerve integrity of a frequently prescribed drug in coronary artery disease.¹⁵ From a clinical perspective, 123I-mIBG could be used to identify high-risk individuals who may most benefit from HMG-CoA reductase inhibition via statins. However, side effects of this drug are rather rare and the most serious adverse event associated with statins is a potentially life-threatening rhabdomyolysis, with an incidence of < 1/1000 patients treated.¹⁶ Given its high safety profile and documented efficacy, statins are one of the most prescribed drugs in the United States, and the most recent guidelines for lipid-lowering therapy has also substantially increased the number of patients eligible for statins.^{9,17} Thus, while the present study corroborates the beneficial effects of this treatment on the cardiac nervous system, it remains debatable whether 123I-mIBG is a useful tool to decide whether statins should be prescribed (i.e. in the vast majority of subjects, it will be prescribed anyway). The retrospective analysis also warrants further confirmation. First, although a propensity score matching both groups has been conducted, it remains unclear why those patients not treated with statins were not eligible for such lipid-lowering medication (either at the beginning of the study or during follow-up). Thus, a selection bias cannot be definitively ruled out, as the potential for an improved cardiac nerve integrity may have been *per se* lower in this particular cohort. Second, a more careful design of future studies is needed, e.g. by performing a baseline 123I-mIBG scan closer to the time of the infarct, which would also verify whether differences in both groups pre-existed. Third, a clear cause and effect relationship cannot be derived from the present data, as the improvement of the SNS could also be caused by either improvement in perfusion or function, which

could impact the HMR. In addition, long-term outcome data, e.g. by LVEF assessments at delayed time-points would further clarify the underlying effect of statins on cardiac nerve integrity.

In clinical practice, there remains a substantial percentage of patients which is statin intolerant,¹⁸ and the pharmacologic options for those individuals has been recently expanded by the proprotein convertase subtilisin kexin type 9 inhibitors (PCSK9i), which facilitate degradation of hepatocyte LDL receptor.¹⁹ Studies such as of *Takahashi* and colleagues may lay the groundwork to assess cardiac nerve integrity in patients treated with PCSK9i as well, which may provide further insights into the beneficial effects of such novel drugs, e.g. to assess whether PCSK9i alone (or in combination with statins) is more beneficial for the cardiac SNS and LV performance. For instance, an 123I-mIBG scan prior to initiation of PCSK9i may be useful to identify appropriate candidates for such novel and expensive therapies and to differentiate between responders and non-responders.^{17,20} However, such an approach would be preferably performed with dedicated myocardial SNS positron emission tomography radiotracers, such as 11C-hydroxyephedrine, 18F-LMI1195, 18F-fluorohydroxyphenethylguanidines, or the recently introduced 18F-AF78.^{21–26} These compounds have been advocated to allow for a more thorough evaluation of the cardiac nervous system, e.g. by assessing regional heterogeneity, such as denervation in the viable border zone of an infarct, instead of a more global assessment of cardiac nerve integrity using 123I-mIBG scintigraphy.²⁷

Taken together, *Takahashi* and colleagues showed that currently prescribed lipid-lowering medication may have an impact on myocardial SNS, which may attenuate cardiac ventricular remodelling, but the present findings may rather not substantially influence decision-making in clinical practice. However, future studies may investigate whether SNS molecular imaging of the heart may hold the potential to identify treatment responders of novel and expensive lipid-lowering medication, preferably in subjects which are intolerant to current statin treatment.

Disclosure

Rudolf A. Werner, James T. Thackeray, and Frank M. Bengel have no conflict of interest to declare.

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