

LETTERS TO THE EDITOR

HbA_{1c} level increases the risk of microvascular and macrovascular complications in patients who have diabetes mellitus.² Further, lowering the HbA_{1c} concentration in patients with type 2 diabetes mellitus decreases the absolute risk of development of coronary artery disease by 5% to 17% and decreases all-cause mortality by 6% to 15%.³ It is clear from the 10-year follow-up of the Diabetes Prevention Program that lifestyle modification and, to a lesser degree, metformin use substantially reduce the development of diabetes mellitus compared with placebo (10-year diabetes mellitus incidence reductions of 34% and 18%, respectively).⁴

The prognostic importance of low HbA_{1c} values is unknown, but the natural assumption of clinicians may be that a low HbA_{1c} level is beneficial in all patients. However, several other studies have reported that low HbA_{1c} concentrations (<4.0%-5.0%) are associated with an increased risk of all-cause mortality in both diabetic and nondiabetic patients.⁵⁻⁷ There may be a threshold below which the HbA_{1c} level is associated with an increased all-cause mortality risk among persons without diabetes; hence, additional research is needed to confirm the ideal HbA_{1c} goal. Moreover there are insufficient data to support a beneficial effect of lowering the HbA_{1c} value in nondiabetic individuals.

In their letter to the editor, Babu et al propose introduction of exercise training in nondiabetic individuals to prevent coronary artery disease. Even though primary prevention measures should be introduced in nondiabetic individuals to prevent coronary artery disease, there are no prospective studies to suggest the target HbA_{1c} goal because targeting HbA_{1c} levels to 4.0% to 5.0% or less may have a deleterious effect. Hence, based on an incremental association of HbA_{1c} value and coronary artery disease and its severity, as observed in our study, we support the early introduction of

primary prevention measures even in nondiabetic individuals. However, prospective studies are needed to address the role of exercise training in nondiabetic individuals and to guide target HbA_{1c} concentrations to obtain maximum benefits while simultaneously avoiding the deleterious effects of very low HbA_{1c} levels.

Nagaraja Moorthy, DM

Sri Jayadeva Institute of Cardiovascular
Sciences and Research
Bangalore, India

Naveen Garg, DM

Aditya Kapoor, DM

Satyendra Tewari, DM

Sudeep Kumar, DM

Archana Sinha, MSc

Anshika Shrivastava, MSc

Pravin K. Goel, DM

Sanjay Gandhi Postgraduate Institute of
Medical Sciences
Lucknow, India

1. Garg N, Moorthy N, Kapoor A, et al. Hemoglobin A_{1c} in nondiabetic patients: an independent predictor of coronary artery disease and its severity. *Mayo Clin Proc*. 2014;89(7):908-916.
2. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321(7278):1677-1686.
3. ten Brinke R, Dekker N, de Groot M, Ikerheim D, Lowening HbA_{1c} in type 2 diabetes results in reduced risk of coronary heart disease and all-cause mortality. *Prim Care Diabetes*. 2008; 2(1):45-49.
4. Diabetes Prevention Program Research Group. 10-Year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study [published correction appears in *Lancet*. 2009;374(9707):2054]. *Lancet*. 2009;374(9702):1677-1686.
5. Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A_{1c} with cardiovascular disease and mortality in adults: the European Prospective Investigation into Cancer in Norfolk. *Ann Intern Med*. 2004;141(6):413-420.
6. Carson AP, Fox CS, McGuire DK, et al. Low hemoglobin A_{1c} and risk of all-cause mortality among US adults without diabetes. *Circ Cardiovasc Qual Outcomes*. 2010;3(6):661-667.
7. Selvin E, Coresh J, Golden SH, Brancati FL, Folsom AR, Steffes MW. Glycemic control and coronary heart disease risk in persons with and without diabetes: the Atherosclerosis Risk in Communities Study. *Arch Intern Med*. 2005;165(16):1910-1916.

<http://dx.doi.org/10.1016/j.mayocp.2015.01.002>

Coenzyme Q10 and Statin-Induced Myopathy—I

To the Editor: The meta-analysis and review by Banach et al¹ published in the January 2015 issue of *Mayo Clinic Proceedings* presented interesting but disappointing results for those who hoped that coenzyme Q10 (CoQ10) would prove to be the antidote for the muscle pains and myopathy induced by statin use in susceptible patients.

The authors noted that the human body contains about 2 g of CoQ10, of which 500 mg must be replaced each day by diet or endogenous production. Statins interfere with the enzymatic synthesis of CoQ10 and further lower serum CoQ10 levels by reducing the number of low-density lipoprotein particles available to transport CoQ10.

Of the 6 studies included in Table 1 in the article, 1 gave patients 400 mg per day of CoQ10, 2 gave 200 mg of CoQ10 per day, 1 gave 60 mg twice per day, and 2 gave 100 mg per day. Thus, none of the trials tested giving patients their entire daily de novo requirement of CoQ10 (500 mg). How can we be sure that, even in the trial that tested the highest dose of supplemental CoQ10 (400 mg), the entire daily de novo requirement of 500 mg was being met, in the face of statin-reduced synthesis and transport of CoQ10? In the other 5 trials, which supplemented only 200 mg or less of CoQ10 per day, there may have been even larger deficits of CoQ10 because of the smaller supplemental dosages given.

I suggest that a randomized trial of CoQ10 supplementation be conducted, testing whether a dosage of 1 g twice per day ameliorates statin-induced myopathy in order to eliminate the possibility of undersupplementation. If a dosage of 2 g per day reduces myopathy, then the dosage could be reduced until myopathy begins to appear again, thus defining the

minimum effective dosage of CoQ10 supplementation.

The lack of a dose-response effect observed between CoQ10 dosage and myalgias or serum creatine kinase levels could still be consistent with benefit from CoQ10 if the dose-response curve is not linear but rather a threshold effect (step function), whereby no benefit is seen from CoQ10 supplementation until a certain threshold dosage is exceeded. If that threshold dosage turns out to be greater than 400 mg, it would explain why no benefit was seen in this meta-analysis: perhaps too little CoQ10 was administered.

David L. Keller, MD
Torrance, CA

1. Banach M, Serban C, Sahebkar A, et al: Lipid and Blood Pressure Meta-analysis Collaboration Group. Effects of coenzyme Q10 on statin-induced myopathy: a meta-analysis of randomized controlled trials. *Mayo Clin Proc.* 2015;90(1):24-34.

<http://dx.doi.org/10.1016/j.mayocp.2015.01.006>

Coenzyme Q10 and Statin-Induced Myopathy—II

To the Editor: Myopathy is a major clinical problem that contributes considerably to statin therapy discontinuation. Banach et al¹ must be commended for their meta-analysis of randomized controlled trials (6 studies with 302 patients) investigating the impact of coenzyme Q10 (CoQ10) on statin-induced myalgia. They concluded that the results do not suggest any significant benefit: CoQ10 supplementation had no significant effect on muscle pain despite a trend toward a decrease (standardized mean difference, -0.53). Could they explain why they also concluded that “larger, well-designed trials are necessary to confirm the findings from this meta-analysis”? First, there is little rationale for CoQ10 supplementation, as no studies

have found a correlation between intramuscular CoQ10 levels and statin-induced myopathy. Moreover, CoQ10 supplementation induced a trend toward an increase in plasma creatine kinase activity in their study (mean difference, 11.69 U/L). Second, although the trend toward a decrease in muscle pain could be significant with more patients, could it be clinically relevant? Lastly, there are multiple and effective management options for statin-intolerant patients.²

Alain Brailion, MD, PhD
University Hospital
Amiens, France

1. Banach M, Serban C, Sahebkar A, et al: Lipid and Blood Pressure Meta-analysis Collaboration Group. Effects of coenzyme Q10 on statin-induced myopathy: a meta-analysis of randomized controlled trials. *Mayo Clin Proc.* 2015;90(1): 24-34.
2. Abd TT, Jacobson TA. Statin-induced myopathy: a review and update. *Expert Opin Drug Saf.* 2011; 10(3):373-387.

<http://dx.doi.org/10.1016/j.mayocp.2015.01.005>

In reply—Coenzyme Q10 and Statin-Induced Myopathy

We thank Drs Keller and Brailion for their interest in our article.¹ Dr Keller suggests that there is a need to evaluate higher dosages of coenzyme Q10 (CoQ10) (at least 600 mg/d) in patients with statin-induced myopathy (SIM), an issue we mentioned in our meta-analysis. However, actually conducting such a study is problematic. Specifically, a considerable amount of research now depends on the financial interests of the pharmaceutical industry. The limited amount of research on CoQ10 to date¹ probably reflects their current interest and offers a preview of future interest.

Additionally, all cases of SIM are not due to a single cause.^{2,3} It follows that CoQ10 supplements, even if effective, may not benefit all cases of

SIM. Studies evaluating the role of CoQ10 supplements in patients with SIM would have to involve very large numbers of patients and/or exclude SIM not potentially related to CoQ10 deficiency. These requirements have considerable methodological and cost implications. First, SIM/statin intolerance should be classified using a uniform method.^{2,3} Another question is whether higher dosages of CoQ10 have adverse effects.⁴ Contemporary data concerning the administration of CoQ10 at dosages higher than 1200 mg/d are limited.⁴ It is usually recommended to administer up to 400 mg/d of CoQ10 for patients older than 18 years.⁴ Despite the fact that CoQ10 appears to be generally very safe with no major adverse effects, it is known that it may, among other effects, slightly lower blood glucose concentrations, interfere with chemotherapy medications, interfere with antihypertensive and anticoagulant therapies, affect thyroid hormone concentrations, and interact with thyroid hormone replacement therapy.⁴ Thus, studies with high dosages of CoQ10 are needed.¹⁻⁴

We agree with Dr Brailion that there is no definitive link between SIM and CoQ10. Nevertheless, as outlined previously, there is enough evidence to consider this topic further. In our study, the small increase of plasma creatine kinase activity (mean, 11.69 U/L) was not statistically significant, and there was also a wide confidence interval of -14.25 to 37.63 U/L. This means that this topic still needs to be investigated in larger trials with longer follow-up (and at higher dosages of CoQ10).¹

We also agree that there are several options for the management of statin intolerance, but they may not always be effective. For example, we can use ezetimibe after the recently encouraging results of the IMPROVED Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT).⁵ Another choice

may be to correct vitamin D deficiency.² New lipid-lowering drugs may also prove useful in reducing the risk of SIM altogether.⁶

Statin discontinuation (or reducing statin dosage) is a very relevant clinical issue because it may increase the risk of cardiovascular events.⁷ Therefore, we need to continue our efforts to provide optimal treatment of hyperlipidemia while avoiding (or appropriately treating) SIM.

Maciej Banach, MD

Medical University of Lodz
Lodz, Poland

Dimitri P. Mikhailidis, MD

University College London
London, United Kingdom

On behalf of the
Lipid and Blood Pressure Meta-analysis
Collaboration (LBPMC) Group

1. Banach M, Serban C, Sahebkar A, et al: Lipid and Blood Pressure Meta-analysis Collaboration Group. Effects of coenzyme Q10 on statin-induced myopathy: a meta-analysis of randomized controlled trials. *Mayo Clin Proc*. 2015; 90(1):24-34.
2. Michałska-Kaszcak M, Sahebkar A, Mikhailidis DP, et al: Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group. Analysis of vitamin D levels in patients with and without statin-associated myalgia—a systematic review and meta-analysis of 7 studies with 2420 patients. *Int J Cardiol*. 2015;178: 111-116.
3. Vrablik M, Zlatohlavek L, Stulic T, et al: Statin-associated myopathy: from genetic predisposition to clinical management. *Physiol Res*. 2014;63(suppl 3): S327-S334.
4. Gamdo-Maraver J, Cordero MD, Oropesa-Ávila M, et al: Coenzyme Q10 therapy. *Mol Syndromol*. 2014; 5(3-4):187-197.
5. Cannon CP. IMPROVE-IT Trial: a comparison of ezetimibe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes after acute coronary syndromes. Paper presented at: American Heart Association 2014 Scientific Sessions, November 17, 2014, Chicago, IL.
6. Dragan S, Serban MC, Banach M. Proprotein convertase subtilisin/kexin 9 inhibitors: an emerging lipid-lowering therapy [published online ahead of print June 17, 2014]. *J Cardiovasc Pharmacol Ther*. <http://dx.doi.org/10.1177/1074248414539562>.
7. Tziomalos K, Athyros VG, Mikhailidis DP. Statin discontinuation: an underestimated risk? *Curr Med Res Opin*. 2008;24(11):3059-3062.

<http://dx.doi.org/10.1016/j.mayocp.2015.01.003>

Mayo Clin Proc. ■ March 2015;90(3):415-422
www.mayoclinicproceedings.org

Type A Aortic Dissection in Fibromuscular Dysplasia

To the Editor: Fibromuscular dysplasia (FMD) is a rare, noninflammatory vascular disease characterized by arterial stenosis and aneurysm or dissection most commonly affecting renal, carotid, and vertebral arteries.¹ Although multiple arterial involvement has been described in the literature,²⁻⁵ no surveillance strategies are in place, which often results in catastrophic consequences.

Report of a Case. A 70-year-old woman presented with severe, non-exertional substernal chest pain radiating to the right shoulder. She had

a history of FMD, subarachnoid hemorrhage in 2001, ischemic stroke in 2011, and well-controlled hypertension. Transesophageal echocardiography performed in 2011 for stroke work-up had revealed a borderline dilatation of the ascending aorta measuring 3.5 cm. Her pertinent physical examination results included blood pressure of 136/76 mm Hg, equivalent in both arms, and normal S₁ and S₂ heart sounds without murmur. Electrocardiography revealed ST-segment depression and new T-wave flattening in the lateral leads. Echocardiography illustrated normal left ventricular function with a dilated aortic root (4.3 cm). Urgent cardiac catheterization and

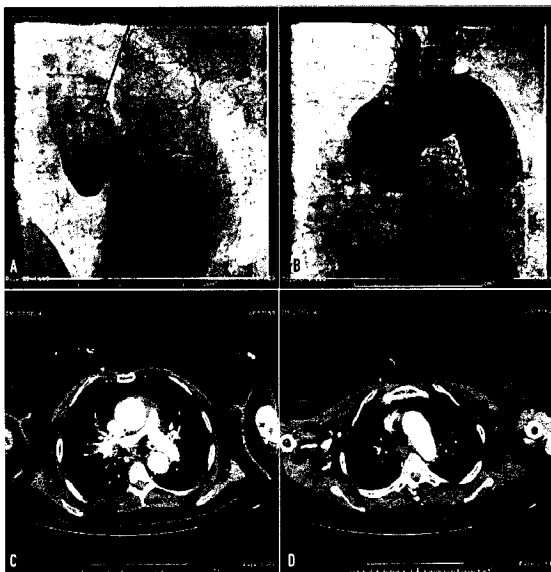


FIGURE. Diagnostic studies in a 70-year-old woman with severe, nonexertional substernal chest pain radiating to the right shoulder. Urgent cardiac catheterization and aortography revealed aortic root dilatation without aortic insufficiency (A, B) and a possible large ascending aortic aneurysm. Computed tomographic angiography of the thorax revealed type A aortic dissection (C, D).