

Towards a Paradigm Shift in Cholesterol Treatment

A Re-Examination of the Cholesterol Issue in Japan

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The authors and the publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

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Preface

Challenging Plasma Cholesterol as a Risk Factor for Cardiovascular Disease

For many years a broad consensus has been established among researchers, health care professionals, medical-scientific societies and governmental bodies who agree that markedly elevated plasma concentrations of cholesterol and low-density lipoprotein (LDL) cholesterol are one among several other causal risk factors for increased occurrence of cardiovascular disorders [1–6]. Different pieces of evidence support a causal role of altered cholesterol metabolism in atherosclerosis development, including epidemiological observations and controlled trials, based primarily on dietary and drug interventions. More recently, studies relating genetic variation with cholesterol metabolism and health outcomes have added weight to the conclusion that elevated LDL cholesterol in plasma is a risk factor for the occurrence of cardiovascular disorders. Certain mutations of the gene encoding for proprotein convertase subtilisin/kexin type 9 (PCSK9), an enzyme that is involved in cholesterol homeostasis induce both a reduced plasma LDL cholesterol and a lowered risk of coronary heart disease [7, 8]. In a large meta-analysis involving data from more than 300 000 people, a variety of genetic polymorphisms that induce lower plasma LDL cholesterol also reduce the risk of coronary heart disease, with a rather consistent reduction of the odds ratio by about 20% for each 0.25 mmol/l or 9.7 mg/dl lowered LDL cholesterol concentration [9]. These and other studies are based on the concept of ‘Mendelian randomisation’, an epidemiological method that assesses the effects of genes considered randomly distributed in the population to obtain unbiased estimates of causation [10]. Moreover, effects of intervention studies provide rather convincing evidence. Several controlled intervention trials have achieved a proportional reduction of the rate of cardiovascular events along with the degree of lowering elevated LDL cholesterol that was reached [11–13]. In subjects with a markedly increased LDL cholesterol level due to a defective LDL cholesterol

receptor function (familial hypercholesterolemia), cholesterol reduction with statins markedly improves the likelihood of event free survival [14]. Based on these and other pieces of evidence, health care professionals around the world treat individuals with primary genetic disorders that induce markedly increased LDL cholesterol plasma concentrations with the goal to reduce blood lipid levels as well as morbidity and mortality. For the general population dietary and lifestyle advice is provided that aims at reducing dyslipidemia and associated risks [5, 6]. However, it is not always adequately appreciated that cholesterol metabolism is only one piece of a complex and multifaceted puzzle of numerous determinants of risk, which also includes the level physical activity, obesity, adiposity, insulin resistance, smoking, different dietary variables e.g. the intake of omega-6 and omega-3 polyunsaturated fatty acids, and many others.

In this supplement, Tomohito Hamazaki and coworkers challenge the largely prevailing view and propose an ‘anti-cholesterol hypothesis’, which appears to be developed primarily from epidemiological observations in the Japanese population, with a number of further added arguments. This thoughtful proposal provides very stimulating reading material. The Editorial Board of the Annals of Nutrition and Metabolism favours the publication of controversial arguments and positions and supports open and unrestricted debates, which may provide the very basis of focussing arguments and of refining our scientific understanding. We wish to emphasize that content published in supplements of our journal is not peer reviewed under the supervision of the Editorial Board, but responsibility lies entirely with the guest editor of the respective supplement.

Berthold Koletzko

Editor in Chief, Annals of Nutrition and Metabolism
for the Editorial Board

References

- 1 Jacobson TA, Ito MK, Maki KC, Orringer CE, Bays HE, Jones PH, et al: National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1 - executive summary. *J Clin Lipidol* 2014;8:473-488.
- 2 Fifth Joint Task Force of the European Society of C, European Association of E, European Association of Percutaneous Cardiovascular I, European Heart Rhythm A, Heart Failure A, European Association for Cardiovascular P, et al: European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur J Prev Cardiol* 2012; 19:585-667.
- 3 Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al: 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129(25 suppl 2): S1-S45.
- 4 Watts GF, Gidding S, Wierzbicki AS, Toth PP, Alonso R, Brown WV, et al: Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation. *Int J Cardiol* 2014;171:309-325.
- 5 Food-and-Agriculture-Organisation-of-the-United-Nations, World-Health-Organisation: Fats and fatty acids in human nutrition. Proceedings of the Joint FAO/WHO Expert Consultation. November 10-14, 2008. Geneva, Switzerland. *Ann Nutr Metab* 2009;55:5-300.
- 6 European-Food-Safety-Authority: Scientific Opinion on Dietary Reference Values for fats, including saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids, trans fatty acids, and cholesterol. *EFSA Journal* 2010;8:1461.
- 7 Cohen JC, Boerwinkle E, Mosley TH, Jr., Hobbs HH: Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med* 2006;354:1264-1272.
- 8 Horton JD, Cohen JC, Hobbs HH: PCSK9: a convertase that coordinates LDL catabolism. *J Lipid Res* 2009;50(Suppl):S172-S177.
- 9 Ference BA, Yoo W, Alesh I, Mahajan N, Mirowska KK, Mewada A, et al: Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. *J Am Coll Cardiol* 2012;60:2631-2639.
- 10 Ebrahim S, Davey Smith G: Mendelian randomization: can genetic epidemiology help redress the failures of observational epidemiology? *Hum Genet* 2008;123:15-33.
- 11 Holme I, Boman K, Brudi P, Egstrup K, Gohlke-Baerwolf C, Kesaniemi YA, et al: Observed and predicted reduction of ischemic cardiovascular events in the Simvastatin and Ezetimibe in Aortic Stenosis trial. *Am J Cardiol* 2010;105:1802-1808.
- 12 Cholesterol Treatment Trialists C, Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, et al: The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012;380: 581-590.
- 13 Nicholls SJ, Tuzcu EM, Sipahi I, Grasso AW, Schoenhagen P, Hu T, et al: Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. *JAMA* 2007;297: 499-508.
- 14 Versmissen J, Oosterveer DM, Yazdanpanah M, Defesche JC, Basart DC, Liem AH, et al: Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. *BMJ* 2008;337:a2423.