JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2014 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 64, NO. 5, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.02.615

Very Low Levels of Atherogenic Lipoproteins and the Risk for Cardiovascular Events

A Meta-Analysis of Statin Trials

S. Matthijs Boekholdt, MD, PhD,* G. Kees Hovingh, MD, PhD,† Samia Mora, MD, MHS,‡ Benoit J. Arsenault, PhD,† Pierre Amarenco, MD,§ Terje R. Pedersen, MD, PhD,‖ John C. LaRosa, MD,¶ David D. Waters, MD,# David A. DeMicco, DPharm,** R. John Simes, MD,†† Antony C. Keech, MBBS, MSc,†† David Colquhoun, MD,‡‡ Graham A. Hitman, MD,§§ D. John Betteridge, MD,‖‖ Michael B. Clearfield, DO,¶¶ John R. Downs, MD,##*** Helen M. Colhoun, MD,††† Antonio M. Gotto, Jr, MD, DPhil,‡‡‡ Paul M. Ridker, MD, MPH,‡ Scott M. Grundy, MD, PhD,§§§ John J.P. Kastelein, MD, PhD†

ABSTRACT

BACKGROUND Levels of atherogenic lipoproteins achieved with statin therapy are highly variable, but the consequence of this variability for cardiovascular disease risk is not well-documented.

OBJECTIVES The aim of this meta-analysis was to evaluate: 1) the interindividual variability of reductions in low-density lipoprotein cholesterol (LDL-C), non–high-density lipoprotein cholesterol (non-HDL-C), or apolipoprotein B (apoB) levels achieved with statin therapy; 2) the proportion of patients not reaching guideline-recommended lipid levels on high-dose statin therapy; and 3) the association between very low levels of atherogenic lipoproteins achieved with statin therapy and cardiovascular disease risk.

METHODS This meta-analysis used individual patient data from 8 randomized controlled statin trials, in which conventional lipids and apolipoproteins were determined in all study participants at baseline and at 1-year follow-up.

RESULTS Among 38,153 patients allocated to statin therapy, a total of 6,286 major cardiovascular events occurred in 5,387 study participants during follow-up. There was large interindividual variability in the reductions of LDL-C, non-HDL-C, and apoB achieved with a fixed statin dose. More than 40% of trial participants assigned to high-dose statin therapy did not reach an LDL-C target <70 mg/dl. Compared with patients who achieved an LDL-C >175 mg/dl, those who reached an LDL-C 75 to <100 mg/dl, 50 to <75 mg/dl, and <50 mg/dl had adjusted hazard ratios for major cardiovascular events of 0.56 (95% confidence interval [CI]: 0.46 to 0.67), 0.51 (95% CI: 0.42 to 0.62), and 0.44 (95% CI: 0.35 to 0.55), respectively. Similar associations were observed for non-HDL-C and apoB.

CONCLUSIONS The reductions of LDL-C, non-HDL-C, and apoB levels achieved with statin therapy displayed large interindividual variation. Among trial participants treated with high-dose statin therapy, >40% did not reach an LDL-C target <70 mg/dl. Patients who achieve very low LDL-C levels have a lower risk for major cardiovascular events than do those achieving moderately low levels. (J Am Coll Cardiol 2014;64:485–94) © 2014 by the American College of Cardiology Foundation.

From the *Department of Cardiology, Academic Medical Center, Amsterdam, the Netherlands; †Department of Vascular Medicine, Academic Medical Center, Amsterdam, the Netherlands; ‡Center for Cardiovascular Disease Prevention, Brigham and Women's Hospital, Boston, Massachusetts; §Department of Neurology and Stroke Center, Bichat University Hospital, Paris, France; ‖Center of Preventive Medicine, Oslo University Hospital, Ulleval and University of Oslo, Oslo, Norway; ¶Health Science Center, State University of New York, Brooklyn, New York; #Division of Cardiology, San Francisco General Hospital and the University of California at San Francisco, San Francisco, California; **Global Pharmaceuticals, Pfizer Inc., New York, New York; ††NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia; ‡‡The Wesley Hospital, Brisbane, Australia; §§Centre for Diabetes, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom; ‖‖Department of Endocrinology and Diabetes, University College Hospital, London, United Kingdom; ¶¶Touro University, Mare Island, California; ##Department of Medicine, University of Texas Health Science Center, San Antonio, Texas; ***VERDICT, South

ABBREVIATIONS AND ACRONYMS

apo = apolipoprotein

CHD = coronary heart disease

CVD = cardiovascular disease

HDL-C = high-density lipoprotein cholesterol

LDL-C = low-density lipoprotein cholesterol

MI = myocardial infarction

non-HDL-C = non-high-density lipoprotein cholesterol

PCSK9 = proprotein convertase subtilisin/kexin 9

There is a wealth of evidence that high-dose statin therapy reduces both levels of atherogenic lipoproteins and cardiovascular disease (CVD) risk beyond that achieved with usual-dose statin therapy (1). However, the evidence on the efficacy of statin therapy is interpreted on the basis of mean reductions of low-density lipoprotein cholesterol (LDL-C) and mean reductions of CVD risk within randomized trials. There is large interindividual variation in the extent of reduction of atherogenic lipoprotein levels achieved with statin therapy. Post-hoc analyses of randomized trials suggest that the benefits of statin therapy depend on the extent of achieved LDL-C reduction (2,3). In addition, patients achieving very low LDL-C levels have been shown to be at very low CVD risk, although the number of patients achieving such very low levels in any given single trial is usually small (4–6).

The guideline-recommended marker of atherogenic lipoproteins is LDL-C, but we have recently shown that among patients treated with statin therapy, non-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein B (apoB) are at least as strongly associated with CVD risk (7). Current guidelines consider the target LDL-C level to be in the range of 70 to 130 mg/dl, but observational evidence suggests that this range might be too conservative. Interestingly, novel lipid-lowering therapies, including mipomersen and inhibitors of proprotein convertase subtilisin/kexin 9 (PCSK9), may allow the majority of patients to reach LDL-C levels <70 mg/dl (8–10). However, it is unclear whether pharmacological interventions resulting in atherogenic lipoprotein levels in this anticipated treatment range are beneficial in terms of CVD risk.

SEE PAGE 495

It was therefore our objective with this study to assess: 1) the variability of LDL-C, non-HDL-C, and apoB reduction achieved with established statin therapy; 2) the proportion of patients not reaching guideline-recommended LDL-C, non-HDL-C, or apoB levels despite being treated with high-dose statin therapy; and 3) the association between achieved

Texas Veterans Health Care System, San Antonio, Texas; †††Medical Research Institute, University of Dundee, Dundee, United Kingdom; ‡‡‡Weill Cornell Medical College, New York, New York; and the §§§Center for Human Nutrition, Southwestern Medical Center, University of Texas, Dallas, Texas. This meta-analysis was not supported by any funding. The contributing trials were funded by their respective sponsors and provided the requested data. They did not play any role in the statistical analysis, interpretation of the data, writing of the manuscript, or the decision to submit the manuscript. Dr. Hovingh is funded by a Veni grant (project number 91612122) from the Netherlands Organisation for Scientific Research. Drs. Boekholdt, Hovingh, and Arsenault have received consulting fees from Pfizer Inc. Dr. Hovingh has served on the speakers' bureaus of Amgen Europe B.V., Genzyme Netherlands, Merck Sharp & Dohme Corporation, Pfizer B.V., Roche Nederland B.V., and Sanofi-Aventis Netherlands B.V. Dr. Mora has received honoraria grants through her institution from Atherotech Diagnostics, AstraZeneca Pharma U.S., Inc., and the National Heart, Lung, and Blood Institute (HL117861); consulting fees from Cerenis Therapeutics, Genzyme Corporation, Pfizer Inc., and Quest Diagnostics Inc.; and travel accommodations/meeting expenses from Pfizer Inc.; and has served on the speakers' bureaus of Abbott Laboratories and AstraZeneca Pharma U.S., Inc. Dr. Amarenco has served on the speakers' bureaus of AstraZeneca France, Boehringer Ingelheim France S.A.S., Merck KGaA, Pfizer Inc., Sanofi-Aventis, and the government of France; and has received consulting fees from AstraZeneca France, Bayer S.A.S., Boehringer France S.A.S., Boston Scientific-France, Bristol-Myers Squibb Agen, Daiichi Sankyo France S.A.S., Edwards Lifesciences S.A.S., Kowa Europe GmbH, H. Lundbeck A/S, Merck KGaA, and Pfizer Inc. Dr. LaRosa has received consulting fees from Amgen Inc. and Pfizer Inc.; and travel expenses from Pfizer Inc. Dr. Pedersen has received honoraria grants and/or served on the speakers' bureaus of AstraZeneca Pharma U.S., Inc., Merck Sharp & Dohme Corporation, Pfizer Inc., and Roche Therapeutics Inc. Dr. Waters has received consulting fees from Anthera Pharmaceuticals Inc., Genentech U.S.A., Inc., Pfizer Inc., Roche Therapeutics Inc., and Laboratoires Servier; has served on the speakers' bureaus of Pfizer Inc. and Zydus Cadila Healthcare Ltd. (Medica); and has participated in committees of clinical trials sponsored by Aegerion Pharmaceuticals, Inc., BioSante Pharmaceuticals, Inc., Merck & Co., Inc., Pfizer Inc., and Sanofi-Aventis. Dr. DeMicco is an employee of, and holds stock options in, Pfizer Inc. Prof. Keech has received honoraria grants from and/or served on the speakers' bureaus and/or advisory boards of Abbott Australasia Pty. Ltd., AstraZeneca Australia, Bristol-Myers Squibb Australia, Eli Lilly Australia, Merck KGaA, Novartis A.G., Pfizer Inc., Roche Products Pty. Ltd., and Solvay Interox Pty. Ltd. Dr. Hitman has received consulting fees from and/or served on the speakers' bureaus of AstraZeneca, Eli Lilly and Co. Ltd., GlaxoSmithKline plc., Merck Sharp & Dohme Ltd., Novo Nordisk Ltd., OSI Pharmaceuticals Ltd., Pfizer Inc., and Takeda U.K. Ltd.; and has received honoraria grants from Parke-Davis and Eli Lilly and Co., Ltd. Dr. Betteridge has served on the speakers' bureaus and/or advisory boards for Aegerion Pharmaceuticals, Inc., Amgen Europe B.V., AstraZeneca, Janssen Ltd., Kowa Europe GmbH, Merck Sharp & Dohme Ltd., Pfizer Inc., Roche Products Ltd., Sanofi-Synthelabo Ltd., and Takeda U.K. Ltd. Dr. Clearfield has received honoraria for consulting on the advisory boards for AstraZeneca Pharma U.S., Inc., and Merck Sharp & Dohme Corporation. Dr. Colhoun has received honoraria grants through the E.U. Innovative Medicines Initiative from AstraZeneca, Boehringer Ingelheim Ltd. U.K., Eli Lilly and Co., Ltd., JRDF, Pfizer Inc., Roche Products Ltd., and Sanofi-Aventis; consulting fees from Eli Lilly and Co., Ltd., Novartis Pharmaceuticals U.K. Ltd., Pfizer Inc., and Sanofi-Aventis; has served on the speakers' bureaus of, and received travel expenses from, Pfizer Inc.; served on the advisory boards of Eli Lilly and Co., Ltd., Novartis Pharmaceuticals U.K. Ltd., Pfizer Inc., and Sanofi-Aventis; holds stock options in Roche Products Ltd.; and has participated in committees of clinical trials sponsored by Eli Lilly and Co., Ltd., JDRF, Novartis Pharmaceuticals U.K. Ltd., and Sanofi-Aventis. Dr. Gotto has received