Natural Statins and Stroke

To the Editor:

The comprehensive review by Furberg1 of natural statins and stroke raises a number of issues. Stroke was a secondary end point in these studies in patients with cardiovascular disease (CVD). Primary end-point trials in stroke are awaited. Surrogate markers can be valuable guides to the introduction of better therapies before large-scale trials are completed. LDL may be the best surrogate marker of prognosis in CVD. In stroke, the primary role of LDL is less clear, but the subgroup analyses and the association of LDL reduction with mechanisms of plaque stabilization imply the need for effective therapy. The new target of LDL <100 mg/dL (<2.5 mmol/L) may be difficult to achieve with some natural statins. The extent to which comparative trials between statins are necessary to demonstrate a class effect is debatable, as they seem to share many ancillary actions.2

The effects of statins on fibrinogen are controversial. Epidemiological evidence suggests fibrinogen is an independent risk factor, but it is unnecessary as an additional predictor in models of CVD risk. No clinical trials have demonstrated that a reduction in fibrinogen alone will reduce events or the converse. In contrast to the non–peer-reviewed communication cited with its claimed 50% increase in fibrinogen,1 we have published observational data of 19% to 23% median increases in fibrinogen with atorvastatin in 89 patients with familial hyperlipidemias3 and a subset of 21 patients at high risk of CVD.4 We have extended these observations to 201 patients with familial hyperlipidemias and have found a median increase of 13% (range −25% to 63%) at 12 weeks with atorvastatin 10 to 80 mg. Previously, 98 of the same patients showed a 5% median decrease (range −28% to 28%) in fibrinogen when initially treated with simvastatin 20 to 40 mg. The effects of atorvastatin seen in our studies contrast with data from larger randomized, placebo-controlled trials in different but commoner patient groups.5 Our observations need to be investigated in randomized, placebo-controlled trials in specified patient groups, and any drug specificity or time course needs to be determined.3–5 The consequences of large reductions in LDL as opposed to small rises in fibrinogen are unknown. However, LDL seems to be a stronger predictor of risk than fibrinogen.

Until evidence on interventions affecting fibrinogen is available, decisions on drug therapy need to be made in the light of available trial data. Currently, that means the most cost-effective, least side-effect–prone, evidence-based method of achieving LDL, and secondarily HDL and triglyceride, targets.

Anthony S. Wierzbicki
Senior Lecturer in Chemical Pathology
St. Thomas’ Hospital
London, UK

Martin A. Crook
Senior Lecturer in Chemical Pathology
St. Thomas’ Hospital
London, UK

Dimitri P. Mikhailidis
Reader in Chemical Pathology
Anthony F. Winder
Professor of Chemical Pathology
Royal Free Hospital
London, UK


Response

Wierzbicki et al support the view that the statins differ in their nonlipid actions; atorvastatin, in contrast to simvastatin, raises fibrinogen. The authors call for randomized clinical trials to determine the clinical importance of this finding.

In a surprising development within a week of the publication of the editorial,1 the Food and Drug Administration (FDA) took action against a claim that statins can be used interchangeably. Its Division of Drug Marketing, Advertising, and Communications issued a Warning Letter2 to Novartis for a “false or misleading” TV advertisement suggesting that its product “Lescol is similar in effectiveness to other cholesterol lowering agents including Pravachol, Mevacor, and Zocor, and that the only difference between these agents is cost.” The agency pointed out that it has not been demonstrated that Lescol reduces cardiovascular morbidity and mortality and that “because of dosing differences, Lescol may cost more than the other agents.” This action by the FDA has raised an interesting question. How will the agency apply the criteria behind this Warning Letter to other statins and other drug classes for which the primary documentation for efficacy is change in a surrogate outcome (surrogate efficacy)?

Curt D. Furberg, MD, PhD
Professor
Wake Forest University
School of Medicine
Winston-Salem, NC

Natural Statins and Stroke
Anthony S. Wierzbicki, Martin A. Crook, Dimitri P. Mikhailidis and Anthony F. Winder

Circulation. 2000;101:e45
doi: 10.1161/01.CIR.101.3.e45
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/101/3/e45

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/