

Editorial

Pleiotropic Effects of Statins: Implications for a Wide Range of Diseases

Kosmas I. Paraskevas¹, Vassilios Stathopoulos² and Dimitri P. Mikhailidis¹

¹*Department of Clinical Biochemistry (Vascular Disease Prevention Clinic), Royal Free Hospital and Royal Free Medical School, University College London (UCL), University of London, London, UK;* ²*2nd Department of Surgery, "Agia Olga" Hospital, Athens, Greece*

INTRODUCTION

The discovery of specific inhibitors of 3-hydroxy-3-methyl-glutaryl CoA synthase 3 decades ago led to the introduction of statins [1,2]. Statins primarily inhibit cholesterol biosynthesis; this explains their key role in the management of hypercholesterolemia and other dyslipidemias [3–7]. Combination with other lipid lowering agents (e.g. fibrates or ezetimibe) may be required to produce the optimal outcome [3–7].

Despite pharmacokinetic differences between the several statins available, these drugs are effective and safe [8,9]. Cerivastatin is the only exception; this agent was withdrawn in 2001 due to an excess of deaths attributed to drug-associated rhabdomyolysis [10].

Cardiovascular risk reduction with a statin is probably associated with the extent of the increase in high-density lipoprotein cholesterol (HDL-C) and triglyceride levels independently from the degree of low-density lipoprotein cholesterol (LDL-C) reduction [11–13]. These findings suggest that the effect of statins on both HDL-C and triglyceride levels is clinically relevant.

Other effects of statins use include oxidative stress and cytokine levels reduction [14–17]. These beneficial effects and endothelial activation may appear very rapidly (after 2h) after initiation of treatment [14].

STATINS AND INDICATIONS RELATED TO THE CARDIOVASCULAR SYSTEM

A number of recent studies suggest that statins may have an effect on heart failure [18,19], stroke [20,21] and acute coronary syndromes [22]. For example, statins may inhibit/reverse myocardial remodeling, decrease inflammation, improve endothelial dysfunction and restore autonomic nervous system balance in patients with heart failure [18,19]. In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, patients with a recent stroke or transient ischemic attack without coronary heart disease receiving atorvastatin 80 mg/day had a significant 16% relative risk reduction of stroke and a 35% reduction in the risk of major coronary events compared with the placebo group

[21]. However, routine statin use in patients with asymptomatic carotid artery atherosclerosis may neither reduce the incidence of cerebrovascular events nor be cost-effective [23]. Furthermore, a recent trial, the Controlled Rosuvastatin in Multinational Trial in Heart Failure (CORONA), did not show any significant reduction in events in patients with heart failure assigned to rosuvastatin as compared with placebo [24].

Statins are an essential component of the treatment of vascular disease [25–31] since their use is associated with a reduction in events in these patients [25–31]. Other beneficial effects have also been reported; for example, in patients with peripheral arterial disease (PAD), statins improve the associated symptoms (e.g. walking distance) [25]. In patients with carotid artery disease, statins significantly reduce carotid intima-media thickness progression and stroke/transient ischemic attack rates [27]. Furthermore, they improve perioperative, as well as long-term, morbidity and mortality should these patients undergo surgery [26]. Lipid-lowering drugs were also protective for both late freedom from progression of disease [Odds Ratio (OR), 0.202; $P < 0.0002$] or late anatomic failure (OR, 0.128; $P < 0.0003$) after carotid endarterectomy [32].

Although not widely appreciated, the beneficial effects of statins on renal function in vascular patients are of clinical interest [33–37]. Impaired renal function per se predicts vascular risk and statins improve renal function (as determined by plasma creatinine, cystatin C and urate levels, calculated creatinine clearance and microalbuminuria) [33–37]. Elevated creatinine (OR, 1.719; $P < .001$) also correlated with early restenosis after carotid endarterectomy [32]. Impaired renal function and vascular disease may progress in parallel [33–38].

STATINS AND EMERGING INDICATIONS

In the past few years, several novel indications for statin therapy have emerged [38–44]. These potential "emerging" indications of statins are reviewed elsewhere [45]. These include osteoporosis, cancer, solid organ transplantation, various neurological disorders, (such as Alzheimer's disease, Parkinson's disease and multiple sclerosis), cardiac arrhythmias, rheumatoid arthritis, autoimmune diseases, sepsis and allergic asthma [45–47]. Patients undergoing surgical operations may also benefit from preoperative statin therapy [48,49]. Emerging benefits of statin use in these patients include (among others) a reduction in postoperative infec-

*Address correspondence to this author at the Department of Clinical Biochemistry (Vascular Disease Prevention Clinic), Royal Free Hospital Campus, University College London, Pond Street, London NW3 2QG, UK; Tel: +44 (0) 20 7830 2258; Fax: +44 (0) 20 7830 2235; E-mail: MIKHAILIDIS@aol.com

tions and possibly postoperative intra-abdominal adhesion formation without a concomitant effect on anastomotic healing [49]. This latter effect is exerted partly by up-regulation of fibrinolysis [49]. Future trials may confirm these preliminary data.

These non-lipid-related effects of statins are referred to as “statin pleiotropy” [50–52]. These “pleiotropic” effects include improving endothelial function, enhancing the stability of atherosclerotic plaques, inhibiting the thrombogenic response as well as decreasing oxidative stress and vascular inflammation. However, the pleiotropic effects of statins have been viewed with scepticism by some [53].

Although only preliminary evidence is currently available for some indications [45], the potential for statin use in the majority of these “emerging” indications seems promising. Statins are not “a panacea for all illnesses” [53]. Nevertheless, the established beneficial effects of long term statin use in dyslipidemic and vascular patients should justify their use in a large number of patients. These patients may then benefit from any “additional” effects of statins.

CONFLICTS OF INTEREST

Dr. Mikhailidis is a member of the Guidelines Committee of the European Society for Vascular Surgery. He has received honoraria for lectures and advisory boards as well as travel and research grants from AstraZeneca, Bristol-Myers Squibb, Glaxo-SmithKline, Merck KGaA, Merck, Sharp & Dohme, Novartis, Pfizer, Sanofi-Aventis, Schering-Plough, Solvay-Fournier and Otsuka.

Dr. Paraskevas and Dr. Stathopoulos have no conflicts of interest.

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