A major pharmaceutical success story of the late 20th century was the introduction of statins into clinical medicine. This class of drugs (the firefighters) has contributed to reduced morbidity and mortality from atherosclerotic cardiovascular disease by lowering total cholesterol levels, particularly low-density lipoprotein (LDL) cholesterol (the arsonists), and also by raising high-density lipoprotein cholesterol levels, albeit less dramatically. Triglyceride levels may also be reduced. The success of this approach in older adults has also led to the controversial proposal to begin statin therapy even earlier in younger individuals with elevated lipid levels. Other benefits have also been attributed to statins, including the effects on inflammatory and immune responses after myocardial infarction. Despite this success story, statins are not a panacea. Some patients experience adverse reactions such as myositis that preclude their taking optimal doses and, in some instances, prevent statin use altogether. Much less commonly, statins can lead to rhabdomyolysis, especially in combination with drugs such as gemfibrozil.

More recently, the US Food and Drug Administration mandated a change in labeling that warns consumers that statins can lead to poorer control of blood glucose levels in patients with type 2 diabetes mellitus. Alternative approaches to the treatment of elevated cholesterol levels, for example, therapy with niacin or drugs that influence cholesterol metabolism such as ezetimibe, have also failed in randomized clinical trials or fallen out of favor because of the relatively weak strength of evidence.

In this issue of Circulation, Chatterjee et al describe an additive or alternative experimental approach to statin therapy. Sphingosine is an unsaturated 18-carbon alcohol that forms the backbone of sphingolipids, which are essential for normal cell membrane structure and function. Sphingolipid metabolites include ceramide and sphingosine 1-phosphate (S1P), signaling molecules considered to have opposing effects, ceramide being proapoptotic and S1P being prosurvival. The ceramide biosynthetic pathway includes the transformation of ceramide into glucosylceramide and lactosylceramide by specific transferase enzymes (Figure). It has been known for several decades that these glycosphingolipids (GSLs) are present in human plasma. GSLs such as lactosceramide are also found in excess in atherosclerotic plaque intima and have been implicated in aortic smooth muscle cell proliferation.

Inhibitors of GSL synthesis that exhibit a profound effect on lipid metabolism have been developed. Among these is N-(5′-adamantane-1’-yl-methoxy)-pentyl-1-deoxynojirimycin, which is also a glucocerebrosidase inhibitor.

The mechanisms whereby GSL synthesis inhibition influences cholesterol metabolism and atherosclerosis have been previously investigated. For example, in human foam cells and macrophages, the GSL lactosceramide resulted in cholesterol sequestration can be stimulated by GSLs in late endosomes/lysosomes. Subsequently, Glaros et al reported that PDMP enhanced cholesterol export from cholesterol laden macrophage foam cells via ABCA1. As noted above, Chatterjee et al also described an increase in the mRNA for this transporter in response to D-PDMP treatment. Other transporters similarly affected included the aforementioned CD36 and SR-B1. D-PDMP also enhanced cholesterol metabolism via

The Perpetual Inflammatory Civil War for Survival

Joel S. Karliner, MD
the LDL receptor pathway as evidenced by increases in LDL receptor protein mass and elevated expression of the sterol regulatory element-binding protein. In vascular smooth muscle cells, PDMP has also been reported to enhance interleukin-1β stimulation of nitrite, thereby providing an additional mechanism whereby this GSL may be of benefit in atherosclerotic vessels.

The first rate-limiting step in the sphingolipid biosynthetic pathway is the formation of 3-keto-dihydrosphingosine from serine and palmitoyl coenzyme A catalyzed by serine palmitoyltransferase. Myriocin, a natural product isolated from the plant *Isaria sinclairii*, inhibits this enzyme and exhibits immunosuppressive activity. Chemical derivatization of myriocin yielded FTY720, an S1P1 and S3 receptor agonist, which is an US Food and Drug Administration–approved drug for the treatment of multiple sclerosis in humans. It became of interest to determine if FTY720 could retard the development of atherosclerosis. In 2 studies, one in LDL receptor–deficient mice16 and another in ApoE null mice, 17 FTY720 was indeed reported to significantly reduce atherosclerosis. Subsequently, Poti et al18 reported that KRP-203, a selective S1P receptor type 1 agonist, ameliorated atherosclerosis in LDL receptor−/− mice without affecting lipid levels. In the latter study, there was extensive reduction of inflammatory markers.

In a more recent report, Wang et al19 studied *ApoE*<sup>R61<sup>h/h</sup></sup> mice that express a form of mouse apolipoprotein E that closely resembles the native mouse protein at 5% of normal plasma levels. These *ApoE*<sup>R61<sup>h/h</sup></sup> mice, also known as HypoE mice,20 were bred to mice deficient in SR-B1. The HypoE allele predisposes to diet-induced hyperlipidemia20 that causes occlusive coronary atherosclerosis and myocardial infarction when the resulting *ApoE*<sup>R61<sup>h/h</sup>/SRB1<sup>−/−</sup></sup> mice are fed a diet rich in fat and cholesterol. Wang et al19 then asked whether FTY720 placed in the drinking water could retard atherosclerotic obstruction of coronary arteries and aortic root atherosclerosis, as well. In the *ApoE*<sup>R61<sup>h/h</sup>/SRB1<sup>−/−</sup></sup> mice, mortality was high during 4 weeks of high-fat, high-cholesterol feeding in comparison with animals fed the same diet plus FTY720 (34% versus 5%, P<0.02).

Similar to the study of Poti et al,18 there was no reduction in serum lipids, nor were any effects on coronary or aortic root atherosclerosis observed. Similar to the results reported by Poti et al, there was also a marked alteration of immune responses. Thus, Wang et al19 noted reduced numbers of T and B cells, and an increased proportion of Tregs. A remarkable new finding was that, in addition to enhancing longevity, FTY720 surprisingly and substantially improved left ventricular function measured by serial echocardiography that could have been a consequence of immunosuppression.19 This observation suggests that S1P1 agonism could be useful in the treatment of heart failure.

In summary, the report by Chatterjee et al emphasizes the importance of biochemical arson as a key element in the pathogenesis of atherosclerosis, and the current article and other recently published data provide evidence that the manipulation of immune system responses can damp down the flames responsible for these conflagrations.

**Acknowledgments**

I thank Robert Raffai, PhD, for helpful comments and Norman Honbo, MA, for preparing the Figure.

---

**Figure.** Shown in schematic format is the pathway leading to glucosylceramide. De novo synthesis of ceramide begins with the condensation of palmitate and serine to form 3-keto-dihydrosphingosine (not depicted). The latter is reduced to dihydrosphingosine followed by acylation to yield dihydroceramide, which in turn generates ceramide via the action of desaturases. Ceramide is at the hub of several pathways, because it can be transformed into sphingomyelin, sphingosine, and sphingosine 1-phosphate, ceramide 1-phosphate, or glucosylceramide. As noted in the text, glucosylceramide (and lactylceramide) foster cellular cholesterol accumulation and reduce cholesterol export. D-PDMP inhibits these actions of glucosylceramide, retarding cholesterol accumulation and enhancing cholesterol export via transporter molecules such as SR-B1, CD36, and ABCA1. CDase indicates ceramidase; CerS, (dihydro)ceramide synthase; CK, ceramide kinase; D-PDMP, D-threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol; GCase, glucosyl ceramidase; GCS, glucosyl ceramide synthase; SK, sphingosine kinase; SMase, sphingomyelinase; SMS, sphingomyelin synthase; SPPase, sphingosine phosphate phosphatase; and SPT, serine palmitoyl transferase.
Sources of Funding
Dr Karliner received grant R01 HL 090606 from the National Heart, Lung, and Blood Institute.

Disclosures
None.

References


Key Words: Editorials ◼ atherosclerosis ◼ cholesterol ◼ fingolimod ◼ glycosphingolipids ◼ hydroxymethylglutaryl-CoA reductase inhibitors ◼ sphingosine
Arsonists and Firefighters: The Perpetual Inflammatory Civil War for Survival
Joel S. Karliner

_Circulation_. 2014;129:2368-2370; originally published online April 7, 2014;
doi: 10.1161/CIRCULATIONAHA.114.010006
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 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/129/23/2368

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/