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Statins: a preventive strike against sepsis in patients with cardiovascular disease?

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In today's *Lancet*, Daniel Hackam and co-authors[1] report that statin therapy in patients with cardiovascular disease is associated with a reduced rate of sepsis, severe sepsis, and fatal sepsis. Statins are well established as lipid-lowering drugs. Cardiovascular morbidity and mortality are significantly reduced by primary and secondary prevention with statins, as well as by acute therapy with a statin.[2–5]

While lipid lowering itself was initially thought to be responsible for the beneficial effects of statins in cardiovascular disease, more recent findings have suggested that pleiotropic effects of statins—eg, anti-inflammatory and antioxidative properties, modulation of cellular immunity, improvement of endothelial function, or increased bioavailability of nitric oxide—might contribute. Notably, most of these effects are independent of lipid lowering, and seem to be mediated by interference with isoprenoid synthesis and subsequent geranylation of membrane proteins. For instance, blockade of the isoprenoid pathway modulates immune-cell responses by inhibiting the expression of coagulation factors, chemokines, MHC II, and adhesion molecules. Some statins directly antagonise adhesion receptors independently of isoprenoid metabolism.[6,7] Statins have also been shown to exert direct antichlamydial effects during pulmonary infection with *Chlamydia pneumoniae* in mice.[8] The benefit of the drugs might also extend to fungal and viral pathogens.[9] They might even hold promise against the potential threat of an influenza pandemic.[10]

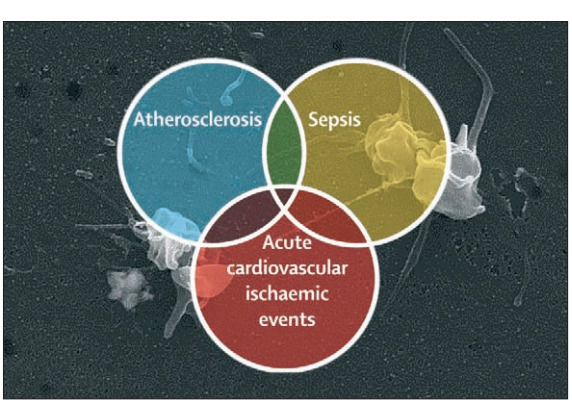

Figure: **Overlapping benefit of statins in patients with atherosclerosis at risk for recurrent acute cardiovascular events, severe sepsis, or both**
Cells in background are activated platelets.

Among many clinical and experimental approaches undertaken to curb the lethal toll of sepsis, activated protein C and low-dose hydrocortisone have, to date, emerged as the only inflammation-modulating substances to benefit patients with severe sepsis.[11,12] In view of their strong effect on inflammation, statins may represent a desirable enforcement in the battle against the increasing incidence and morbidity of severe sepsis and septic shock in developed countries. Indeed, studies in animals[13] and observational reports[14,15] provide evidence in support of this notion. In a prospective cohort study[16] in 361 patients with acute bacterial infections, previous treatment with statins was associated with a substantially reduced rate of severe sepsis and admission to the intensive care unit. However, this study was not powered to detect differences in mortality.

Benefiting from the unique medical infrastructure with linked administrative databases in Ontario, Hackam and colleagues have produced an impressive observational study by initial evaluation of 141 487 patients with cardiovascular disease, resulting in a well-paired and homogeneous study cohort of 69 168 patients after propensity-based matching. To minimise the risk inherent to any observational study of the conclusion being based on selection bias in the treatment group, the investigators carefully scrutinised and adjusted the data for several possible confounders. Furthermore, to exclude significant bias favouring statin users, they have analysed tracer outcomes (eg, the association between statin therapy and cataract extraction was assessed to check for the lack of

association where no association would be expected) and created an on-treatment analysis by modelling statin exposure throughout follow-up as a time-dependent covariate.

Hackam and co-authors conclude that statin therapy is associated with a considerably decreased rate of sepsis, severe sepsis, and fatal sepsis, even under the most conservative assessment. This protective effect prevailed at both high and low doses of statin and for several clinically important subpopulations, such as patients with diabetes and heart failure. The data strongly suggest an overlapping and potentially cumulative benefit of statins in the preventive treatment of patients with cardiovascular disease (figure). This effect might be related to the coincidence of cardiovascular risk factors, acute manifestations of atherosclerosis, or an increased risk of severe sepsis.

Beyond these intriguing data, several challenges remain. First, large placebo-controlled blinded randomised trials in patients (irrespective of their history) are clearly needed to build a stronger base for this exciting preventive approach. Similarly, adequately designed clinical trials are warranted to consolidate the promising experimental evidence[13] for the therapeutic potential of statins in sepsis treatment. Second, sensitive variables to identify patients at risk need to be developed and validated—eg, populations with increased susceptibility to detrimental inflammation or infection might be unveiled by appropriate biomarker or genetic screening. Third, existing databases should be mined for potential further therapeutic benefits of statin use (with neurodegenerative disorders and viral infections representing promising diseases for exploration). Finally, detrimental effects of statins have been shown in distinct subsets of patients (eg, increased relative risk for fatal stroke in patients with type II diabetes and end-stage renal disease[16]). Thus caution should prevail and the extension of statins' application to new populations of patients should be accompanied by meticulous monitoring of unexpected side-effects.

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We declare that we have no conflict of interest.

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Communicating radiology results

The typical primary-care doctor in the USA receives 800 chemistry reports, 40 radiology reports, and 12 pathology reports a week.[1] 83% of these doctors report delays in receipt of test results, and only 41% indicated they were satisfied with how test results are managed. In as much as a delay in the communication of results to patients sometimes leads to devastating consequences, it is no wonder that patients, particularly those who undergo radiological studies because of unexplained symptoms or physical findings, show great anxiety as they await results. Hamilton Jordan, Chief of Staff in former US President Jimmy Carter's administration, and a survivor of

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