Statins and sepsis in patients with cardiovascular disease: a population-based cohort analysis

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Summary

Background **Atherosclerosis and sepsis share several pathophysiological similarities, including immune dysregulation, increased thrombogenesis, and systemic inflammation. The relation between statins and risk of sepsis in patients with atherosclerosis is unknown.**

Methods **We did a population-based cohort analysis through linked administrative databases in Ontario, Canada, with accrual from 1997 to 2002. We identified 141 487 patients older than 65 years who had been hospitalised for an acute coronary syndrome, ischaemic stroke, or revascularisation, who survived for at least 3 months after discharge. 46 662 (33%) were prescribed a statin within 90 days of discharge, 94 825 (67%) were not. Propensity-based matching, which accounted for each individual's likelihood of receiving a statin, yielded a cohort of 69 168 patients, of whom half (34 584) received a statin and half (34 584) did not.**

Findings **Incidence of sepsis was lower in patients receiving statins than in controls (71·2 vs 88·0 events per 10 000 person-years; hazard ratio [HR] 0·81; 95% CI 0·72–0·91). Adjustment for demographic characteristics, sepsis risk factors, comorbidities, and health-care use gave similar results (HR 0·81; 95% CI 0·72–0·90). The protective association between statins and sepsis persisted in high-risk subgroups, including patients with diabetes mellitus, chronic renal failure, or a history of infections. Significant reductions in severe sepsis (HR 0·83; 95% CI 0·70–0·97) and fatal sepsis (0·75; 0·61–0·93) were also observed. No benefit was noted with non-statin lipid-lowering agents (0·95; 0·75–1·22).**

Implications

Use of statins in patients with atherosclerosis is associated with a reduced risk of subsequent sepsis. Randomised trials of statins for prevention of sepsis are warranted.

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Introduction

Sepsis is an enduring source of morbidity and mortality in the general population. More than a decade ago, a consensus committee of the Society of Critical Care Medicine and the American College of Physicians defined the disorder as the systemic inflammatory response to the presence of infection which, when severe, is accompanied by organ dysfunction or hypotension.[1,2] The prevention of sepsis has gained importance in recent years because sepsis is common and increasing in incidence, the disease carries a high case fatality rate, and the care of affected patients is extremely costly.[3,4]

Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are potent lipid-lowering agents that reduce the risk of cardiovascular events in patients with diabetes mellitus, coronary artery disease, and other forms of atherosclerosis.[5] Although the major mechanism of action is cholesterol lowering, statins have several pleiotropic effects, including anti-inflammatory, immunomodulatory, antioxidant, antithrombotic, and endothelium-stabilising properties.[6–8] These effects are of unknown importance, but might account for the benefits observed in clinical trials of statins in patients with multiple sclerosis, rheumatoid arthritis, and other inflammatory disorders.[9,10]

Findings of studies in animals suggest that statins might also prevent sepsis.[11–14] Several therapeutic interventions for sepsis that have initially shown promise in studies with animals, however, have proven unsuccessful when tested in people. Two small observational studies have suggested a benefit of statins in patients with acute bacterial infection, including decreased progression to severe sepsis[15] and reduced mortality attributable to sepsis.[16] However, these studies were limited by small sample size, inadequate adjustment for confounding, brief follow-up duration, and absence of information on patient adherence. We postulated that statins reduce the incidence of sepsis in a high-risk population with atherosclerosis. We undertook a large-scale, multi-year, population-based cohort study with a comprehensive analysis of sepsis, propensity-based matching to minimise confounding, and tracer analyses to assess the specificity of the findings.

Methods

Setting and patients

We established a retrospective patient cohort by linking multiple administrative health-care databases over 5 years in the province of Ontario. Throughout the study, Ontario was Canada's most populous province with about 12 million inhabitants, of whom 1·5 million were aged 65 years or older. Elderly patients in Ontario had universal access to hospital care, physicians' services, and prescription drug coverage. Additionally, health-care

records could be analysed using encrypted identifiers to track individuals over time. Approval for the study was obtained from the Sunnybrook and Women's College Health Sciences Centre Research Ethics Board and the University of Toronto Health Sciences Research Ethics Board.

This study used four large, validated databases: the Ontario Drug Benefit (ODB) database, which records prescription medications dispensed to all elderly patients in the province; the Canadian Institute for Health Information (CIHI) Discharge Abstract database, which records all hospital admissions including detailed diagnostic and procedural information; the Ontario Health Insurance Plan database, which provides information on physician claims for inpatient and outpatient services; and the Ontario Registered Persons database, which contains vital statistics on all residents.[17–19] These four databases have been used extensively to study population-based health outcomes.[20–23]

See **Online** for webtable 1

We included consecutive patients older than 65 years who were admitted for an acute cardiovascular event or underwent an arterial revascularisation procedure at any hospital in the province during the accrual period (Jan 1, 1997, to Jan 1, 2002). Our study focused on patients with atherosclerosis because guidelines recommended statins for secondary prevention in nearly all such cases.[24-26] The specific atherosclerotic events were acute coronary syndrome (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 410, 411, 413) and acute ischaemic stroke (ICD-9-CM 433, 434, 436). These diagnostic codes have an accuracy of 90–96%.[27,28] The specific revascularisation procedures were coronary artery bypass grafting, percutaneous coronary intervention, peripheral artery bypass grafting, and carotid endarterectomy. These procedures are categorised in the CIHI database according to the Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures, which has excellent predictive validity (for example, an accuracy of 91% for peripheral vascular surgery).[29] The index date was defined as 3 months following the date of discharge from the qualifying hospitalisation. Patients who died in hospital or before the index date were excluded.

Surveillance for statin prescriptions in the ODB database for each patient began on the date of hospital discharge. All elderly patients in Ontario received universal prescription drug coverage from this formulary; moreover, the coding accuracy of information in the ODB database is excellent with an error rate of only 0·7%.[19] The six statins available in Ontario during the study period were atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, and simvastatin. From each prescription, we recorded the drug, dose, quantity dispensed, and number of days supplied. Patients were defined as statin users if they received one or more prescriptions for a statin during the 3 months preceding the index date. Non-users were defined as individuals who did not receive a statin prescription during this 3-month period.

For each patient who initially received a statin, we used propensity-based matching to identify one control who did not receive a statin according to the following protocol.[30] First, propensity scores were calculated for each patient in the entire cohort on the basis of an extensive list of factors potentially related to the use of statins or the risk of sepsis (webtable 1). Second, each statin user was matched to a smaller pool of non-statin-users by sex, age (plus or minus 1 year), and index date (plus or minus 3 months). Third, we selected the control with the closest propensity score (within 0·2 SD) to each statin user in a 1:1 fashion and discarded the remaining controls. Statin users for whom adequate controls could not be identified were also discarded.

Study outcomes

The observation period for each patient began on the index date and continued until death, hospital admission for sepsis, or the end of the study if uneventful (March 31, 2002). Admissions for sepsis were identified by searching the CIHI database for admissions with a diagnosis of sepsis (ICD-9-CM codes 003·1, 036·2 and 038·0–038·9). This definition has been used extensively in population-based and hospital-based studies of sepsis. Moreover, validation data suggest a sensitivity of 88%[31] and a positive predictive value of 89%[32] for confirmed sepsis; for severe sepsis, the positive predictive value was 98%.[33] Patients who had more than one episode of sepsis were analysed according to their first episode.

Statistical analysis

The primary analysis compared patients initially receiving a statin to controls not initially receiving a statin. Crude differences in the risk of sepsis were calculated as hazard ratios using matched Cox regression models and subsequently adjusted for demographic factors, sepsis risk factors, and other covariates (comorbidities and measures of health-care use). We also evaluated the relation of statin use and subsequent sepsis in eight prespecified subgroups: age greater than median; women; diabetes mellitus; past malignant disease; chronic renal failure; previous infections; oral steroid use; and congestive heart failure. All tests were two-tailed with a p value of 0·05 judged to be statistically significant.

We did several sensitivity analyses to test the robustness of our findings. First, we created an on-treatment analysis by modelling statin exposure throughout follow-up as a time-dependent covariate. Second, the definition of sepsis was modified to consider only admissions where sepsis was the most responsible diagnosis for admission, defined as "the one diagnosis which describes the most significant condition of the patient which causes his or her stay in hospital".[34] Third, the follow-up interval was extended to March 31, 2004, to include episodes of sepsis classified by ICD-10. Fourth,

we examined the outcome of severe sepsis, specified as an admission for sepsis with acute organ dysfunction, a definition validated by others.[33,35] Fifth, we evaluated fatal sepsis defined as an admission for sepsis resulting in death within 28 days of admission.

To further explore the possibility of hidden bias we examined several additional outcomes and exposures in the patient cohort. As a test of specificity, the association between statin therapy and subsequent cataract extraction was assessed. The intent of this analysis was to check for the lack of association where no association would be expected.[36,37] As a test of calibration, we assessed the association between statins and the composite outcome of death, acute myocardial infarction, and ischaemic stroke. The intent of this analysis was to check for the presence of an association where one would be expected.[5] Finally, we assessed the relation between other lipid-lowering drugs and sepsis by replicating the entire propensity-based matching process but replacing the exposure with niacin, fibric acid derivatives, and bile acid sequestrants.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

During the 5-year accrual period, we identified 173 410 consecutive patients older than 65 years who were admitted for an acute coronary syndrome, ischaemic stroke, or arterial revascularisation. Of these, 22 101 individuals died during admission and a further 9822 died within 90 days after discharge. Of the 141 487 survivors, 46 662 (33%) received a statin within 90 days of discharge whereas 94 825 (67%) did not. Propensity-based matching then yielded a final cohort of 69 168 patients, of whom 34 584 received an initial statin prescription and 34 584 did not.

Statin users and controls were very similar in demographic characteristics, sepsis risk factors, other comorbidities, concomitant medications, and health-care use (table 1, webtable 1). The typical participant was a 74-year-old man whose index event was an acute coronary syndrome. The most prevalent comorbidities were diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease, and other structural lung disease. Other important comorbidities were less frequent, including malignant disease, dementia, history of aspiration, and alcoholism. The most common statin prescribed was atorvastatin (12 789, 37%), followed in frequency by simvastatin (9694, 28%), pravastatin (7247, 21%), lovastatin (3367, 10%), fluvastatin (868, 3%), and cerivastatin (619, 2%).

During a mean follow-up of 2·2 years, 551 patients were admitted for sepsis in the statin group and 667 patients in the control group, yielding a total of 1218 episodes. The rate of sepsis was significantly lower for statin-treated patients than controls (71·2 *vs* 88·0 per 10 000 person-years; p=0·0003). The crude hazard ratio for sepsis among statin users compared with non-users was 0·81 (95% CI 0·72–0·91). Adjustment for demographic factors, sepsis risk factors, other comorbidities, and measures of health-care use did not greatly affect this finding (HR 0·81; 95% CI 0·72–0·90). Several other characteristics of patients were also related to the risk of sepsis, including older age, male sex, malignant disease, diabetes mellitus, use of steroids, previous infections, transplantation, chronic liver disease, and renal insufficiency (webtable 2).

See **Online** for webtable 2

Sensitivity analyses revealed similar findings (table 2). In the on-treatment analysis, which adjusted for each individual's adherence to therapy, the association between statin use and risk of sepsis was accentuated. Statin use

	Statin group (n=34 584)	Control group (n=34 584)
Demographic factors		
Age (years)	74·1 (5·5)	74·1 (5·5)
Sex (male)	19 475 (56%)	19 482 (56%)
Index event, coronary	27 072 (78%)	27 120 (78%)
Cerebrovascular	6301 (18%)	6248 (18%)
Peripheral vascular	1211 (4%)	1216 (4%)
Rural residence	5519 (16%)	5501 (16%)
Charlson index (units)	1·3 (1·1)	1·3 (1·2)
Health-care use		
Number of outpatient clinic visits (past year)	35·8 (20·4)	35·7 (20·6)
Number of admissions (past 3 years)	1·7 (1·1)	1·7 (1·1)
Number of medications (past year)	11·5 (5·3)	11·5 (6·0)
Receipt of home care	12 134 (35%)	12 107 (35%)
Length of stay, index admission (days)	8·0 (11·9)	7·9 (9·7)
Risk factors for sepsis		
Malignancy	2488 (7%)	2540 (7%)
Chemotherapy	307 (1%)	324 (1%)
Neutropenia	101 (0·3%)	103 (0·3%)
Diabetes mellitus	10 827 (31%)	10 927 (32%)
Oral steroids	2380 (7%)	2355 (7%)
Antineoplastics	834 (2%)	873 (3%)
Other immunosuppressants	247 (1%)	257 (1%)
History of aspiration	519 (2%)	529 (2%)
Structural lung disease	5058 (15%)	5008 (15%)
Previous infection, respiratory	2296 (7%)	2244 (7%)
Previous infection, genitourinary	2298 (7%)	2255 (7%)
Previous infection, gastrointestinal	211 (1%)	207 (1%)
Previous infection, skin/soft tissue	626 (2%)	618 (2%)
Previous infection, miscellaneous	3345 (10%)	3352 (10%)
Recent trauma	105 (0·3%)	102 (0·3%)
Transplant recipient	168 (1%)	163 (1%)
Other comorbidities		
Heart failure	10 371 (30%)	10 374 (30%)
Stroke	6237 (18%)	6194 (18%)
Chronic liver disease	336 (1%)	325 (1%)
Chronic obstructive pulmonary disease	7937 (23%)	7969 (23%)
Chronic renal insufficiency	3604 (10%)	3565 (10%)
Alcoholism	1150 (3%)	1136 (3%)
Dementia	1994 (6%)	1889 (6%)
Parkinson's disease	4723 (14%)	4678 (14%)

Continuous variables expressed as mean (SD) and categorical variables as n (%).

Table 1: **Baseline characteristics in the matched cohort**

	Hazard ratio (95% CI)
On-treatment analysis	
Univariate	0·57 (0·50–0·63)
Multivariate	0·62 (0·55–0·69)
Sepsis as most responsible diagnosis	
Univariate	0·84 (0·69–1·02)
Multivariate	0·83 (0·68–1·00)
Long-term follow-up	
Univariate	0·85 (0·79–0·93)
Multivariate	0·85 (0·78–0·92)
Severe sepsis analysis	
Univariate	0·83 (0·71–0·98)
Multivariate	0·83 (0·70–0·97)
Fatal sepsis analysis	
Univariate	0·77 (0·62–0·95)
Multivariate	0·75 (0·61–0·93)

Multivariate analyses adjusted for baseline demographics, risk factors for sepsis, other comorbidities, and measures of health-care use.

Table 2: **Sensitivity analyses for statin use and subsequent sepsis**

was also associated with fewer episodes of sepsis compared with controls in the extended duration analysis (mean follow-up 3·8 years) and in analyses that defined sepsis as the most responsible diagnosis accounting for admission. Statin users also had a lower risk of severe sepsis and fatal sepsis than did controls. Furthermore, the risk of sepsis consistently decreased across all eight predefined subgroups (figure). The protective association was evident with both high-dose therapy (HR 0·80) and low-dose therapy (0·81) and was similar for all three of the most prevalent statins (HR range 0·73 to 0·80).

As expected, statin use was associated with a decreased incidence of the composite outcome of death, myocardial infarction, and ischaemic stroke in both crude analyses (HR 0·88; 95% CI 0·85–0·91) and adjusted analyses (0·88; 0·85–0·91). Conversely, statin therapy was not significantly associated with the risk of subsequent cataract extraction in either crude analyses (1·01; 0·97–1·06) or adjusted analyses (1·01; 0·97 to 1·06). Additionally, we noted little evidence for an association between non-statin lipid-lowering drugs and risk of subsequent sepsis in crude analyses (1·02; 0·80–1·30) or adjusted analyses (0·95; 0·75–1·22).

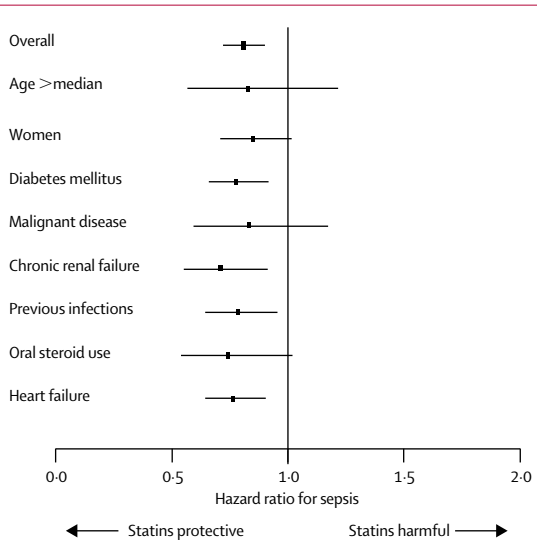

Figure: **Subgroup analyses**
Hazard ratios represent ratio of risk of patients treated with statins to patients not treated with statins as the reference group. Horizontal lines show 95% CI.

Discussion

We observed that the use of statins in patients older than 65 years with atherosclerosis was associated with a 19% reduction in the risk of sepsis. The apparent protective association between statins and sepsis was consistent across several high-risk subgroups, was apparent throughout the entire follow-up period, and was amplified in analyses accounting for non-adherence and crossovers. Moreover, the observed association was in the range of known relative reductions in cardiovascular risk seen in randomised trials of statins and was outside the range of confounding seen in our analyses of tracer outcomes and exposures.

The major limitation of this study was its observational design, which raises the possibility that confounding might have affected the results. In particular, we were unable to determine why certain patients were not prescribed statin therapy. However, four important aspects of the study reduced the likelihood of major confounding. First, we selected a homogenous cohort of patients who all had a recent admission for atherosclerotic cardiovascular disease and therefore were potential candidates for statin therapy. Second, we matched statin users and non-users on many factors related to statin use or the risk of sepsis; moreover, all results were further adjusted for these factors. Third, we found consistent reductions in the risk of severe sepsis and sepsis fatalities. Fourth, our analysis of tracer outcomes and exposures did not suggest significant remaining bias favouring statin users.

The results of this study concur with a growing body of human, animal, and mechanistic data on statins and sepsis.[11–16,38–42] In a small prospective cohort study (n=361), patients who received statins at the time of admission for acute bacterial infection had a substantially lower rate of progression to severe sepsis (relative risk 0·13; 95% CI 0·03–0·52) and a reduced need for intensive care (0·30; 0·10–0·95).[15] In a second study of 388 patients with bacteraemia, patients receiving statins had significant reductions in overall mortality (6% *vs* 28%; p=0·002) and attributable mortality (3% *vs* 20%; p=0·010) compared with patients who did not.[16] In both studies, statin users had significantly higher rates of major comorbidities than did non-users, suggesting that co-existing illness was not responsible for the findings.

Several mechanisms might explain the overall results. In animals that were given statins before a sepsis-

provoking challenge, pretreatment led to substantial reductions in inflammatory cytokines and activation of immune cells,[11–13,42] findings which have since been replicated in studies with people.[38,40,41] Statin administration in animals after the onset of sepsis seemed to be less effective.[42] Additionally, statins appear to reduce the overproduction of nitric oxide implicated in the vasodilatation and circulatory collapse of septic shock.[11,12,14] Moreover, statin therapy completely preserved cardiac output and myocardial responsiveness to dobutamine in an animal model of polymicrobial sepsis, changes accompanied by improvements in survival.[12,42] In addition to effects on the host, statins also seem to attenuate the replication and infectivity of several bacterial, fungal, and viral pathogens.[43–45] Some findings suggest that statins exert antioxidant and anticoagulant properties in experimental models of sepsis.[38,39]

We examined the relation between statin use and the incidence of sepsis in elderly patients with symptomatic atherosclerosis and do not know whether our results can be extrapolated to patients in other settings. However, several lines of evidence suggest our findings might not be confined to those with proven atherosclerosis. First, only a minority of patients in previous studies of statins and sepsis had a history of cardiovascular disease (21% and 31%); moreover, concurrent cardiovascular disease was not predictive of outcome in either study.[15,16] Second, previous studies have shown pleiotropic properties of statins in healthy volunteers without significant atherosclerosis.[40,41] Third, findings of randomised trials of effective interventions against sepsis have generally not shown important interactions between cardiovascular comorbidity and treatment efficacy.[46–48]

We used an epidemiological definition of sepsis that captured admissions with a diagnosis of sepsis. The specific ICD-9 codes we used to define our outcome have high specificity and moderate sensitivity compared with the clinical consensus definition of sepsis.[32,33] Moreover, the observed 28-day mortality and prevalence of criteria for severe sepsis agree with findings of hospital-based studies of septic patients. Restriction of the definition to include only cases for which sepsis was the most responsible diagnosis accounting for admission, moreover, still indicated that statin use was associated with a reduced risk of sepsis. Although the use of administrative databases might have resulted in underdetection of sepsis episodes (due to undercoding inherent in these databases), such deficits in sensitivity would tend to bias our results toward the null.[49]

In summary, the use of statins in patients with atherosclerosis was associated with a significantly reduced risk of sepsis, including severe sepsis and fatal sepsis. These findings have possible implications for care of patients in particular circumstances. First, patients with major infections who are already taking statins might be discouraged from stopping their medication, provided that they can be carefully monitored for statin-related toxic effects. Second, and in keeping with findings suggesting that statins reduce perioperative mortality and adverse events, these medications should not be discontinued routinely at the time of high-risk elective surgery. Third, statins might be considered for patients at very high risk for sepsis, particularly if they have cardiovascular risk factors or known cardiovascular disease. In view of the long history of initially promising interventions for the treatment of sepsis, our results warrant testing by future randomised controlled trials.

Contributors

D G Hackam took part in study conception and design, interpretation of results, drafted the initial manuscript, and revision for important content, and obtained funding. M Mamdani participated in study design, interpretation of results, and revision for important content, and obtained funding. P Li contributed to study design, acquisition and interpretation of results, and revision for important content. D A Redelmeier took part in study conception and design, interpretation of results, and revision for important content, and obtained funding.

Conflict of interest statement

We declare that we have no conflict of interest.

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