Lipid-Lowering Therapy With Statins in High-Risk Elderly Patients
The Treatment-Risk Paradox

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Available evidence has demonstrated that the impact of cardiovascular evidence-based therapies is predominantly dependent on patients' baseline risk of future adverse cardiovascular events.1 If physicians are appropriately attuned to the risk profiles of their patients, one might reasonably assume that patients who are at highest baseline risk should be treated most aggressively. Yet, for many cardiovascular therapies, this is not the case.2-6 For example, studies have consistently demonstrated an inverse relationship between treatment propensity and age.2,7 Moreover, patients with multiple chronic conditions are less likely to receive evidence-based therapies than healthier patients with lower illness severity,8 an observation that may relate to high baseline risk and/or concerns about treatment complications. Nonetheless, the extent to which the discordant relationship between baseline risk and treatment propensity is a phenomenon driven by age alone, arguably the most important determinant of baseline risk in the population, is unknown. Furthermore, the extent to which the treatment-risk paradox applies only to extremes of illness severity or, conversely, applies incrementally throughout the entire spectrum of risk is also unclear.

Context The benefits of cardiovascular therapies such as statins for secondary prevention have been well documented, although they may not be optimally used in patients most likely to benefit. Ideally, aggressiveness in the use of these beneficial therapies should correlate with baseline cardiovascular risk.

Objective To examine the association between physicians’ treatment aggressiveness and baseline cardiovascular risk.

Design, Setting, and Patients Retrospective cohort study incorporating the use of multiple linked health care administrative databases covering more than 1.4 million elderly residents of Ontario. We included 396,077 patients aged 66 years or older who had a history of cardiovascular disease or diabetes while undergoing medical treatment and who were alive on April 1, 1998. Baseline cardiovascular risk was derived using a risk-adjustment index in which we modeled probability of death after 3 years of follow-up.

Main Outcome Measure Likelihood of statin use, stratified by baseline cardiovascular risk, after adjusting for age, sex, socioeconomic status, and rural or urban residence.

Results Only 75,617 patients (19.1%) in this secondary prevention cohort were prescribed statins. In patients 66 to 74 years old, the adjusted probabilities of statin prescription were 37.7%, 26.7%, and 23.4% in the categories of low, intermediate, and high baseline risk, respectively. The likelihood of statin prescription was 6.4% lower (adjusted odds ratio, 0.94; 95% confidence interval, 0.93-0.95) for each year of increase in age and each 1% increase in predicted 3-year mortality risk. The influence of age also interacted synergistically with baseline risk on the prescription of statins (P<.001).

Conclusions We found that prescription of statins diminished progressively as baseline cardiovascular risk and future probability of death increased. Since the benefits of a therapy are dependent on the baseline risk, the maximum benefits of statins may not be fully realized until implementation of therapy includes patients at highest risk.

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mandations advocate the use of statins according to individual baseline risk of future cardiovascular events. Accordingly, the primary objective of this study was to examine the association between physician aggressiveness in the prescription of statins among a secondary prevention cohort of elderly patients and baseline risk throughout the entire risk-severity spectrum.

METHODS

System Context
The Canadian health insurance system provides free universal coverage for most hospitals and ambulatory medical services. The Ontario Drug Benefit (ODB) program is a government-funded drug benefit program that covers outpatient drug costs for all Ontario residents aged 65 years or older. Patients are responsible for a dispensing fee of approximately Can $6, but this fee is waived for patients whose annual income falls below a threshold of Can $15,500 (US $1 = Can $1.34 on March 17, 2004).

Data Source
The Geriatric Ontario Longitudinal Database (GOLD) was created by linking several major health care administrative databases with follow-up tracking of mortality over time, regardless of location of death. Briefly, GOLD includes 1.44 million residents aged 66 years or older who were alive in Ontario on April 1, 1998. Unique encrypted patient identifiers were used for linkage in the multiple databases to protect patient confidentiality. We identified previous hospitalizations using the Canadian Institute of Health Information hospital discharge abstracts and identified physician visits and previous cardiac interventions using physician claims data obtained by the Ontario Health Insurance Plan. We used the ODB to obtain information on medication prescriptions within 1 year before cohort inception. Demographic and geographic information was identified using the Registered Persons Database and data from the official 1996 Census. We excluded all non-Ontario residents and those who did not have a valid health card number. The research ethics board of Sunnybrook and Women's College Health Science Center, University of Toronto, approved the study and waived a requirement for informed consent.

Study Cohort
We selected patients at high risk of future cardiovascular events and included patients older than 66 years with a history of cardiovascular disease or diabetes mellitus while undergoing medical therapy. We defined a statin prescription as one in which a patient had been dispensed any prescription for statin medication within the year before the inception of the cohort. Statins covered in the ODB at the time of the study included atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, and simvastatin. We defined cardiovascular disease in the study sample as 1 or more of the following: cardiovascular hospitalization within 5 years, coronary intervention (cardiac catheterization, percutaneous coronary intervention, or coronary artery bypass graft surgery) within 5 years, or angina (defined as concurrent use of nitrates within the year of cohort inception). Using hospital discharge abstracts, a previous cardiovascular hospitalization was defined as an admission with any of the following: unstable angina, myocardial infarction, congestive heart failure, stroke or transient ischemic attack, or peripheral vascular disease (abdominal aortic aneurysm, peripheral vascular surgery, or carotid endarterectomy). A diagnosis of drug-treated diabetes mellitus required receipt of insulin or oral hypoglycemic agents within 1 year before cohort inception. The definitions and codes that were used to identify eligible patients focused on maximizing specificity rather than sensitivity to ensure the construction of a valid secondary prevention cohort. The coding accuracy of acute myocardial infarction, heart failure, and diabetes had positive predictive values of more than 90%. Although individual cholesterol profiles were unavailable, we assumed that most of these patients would be eligible for statin therapy based on the fact that they were all secondary prevention patients. We excluded patients with a history of cancer within 5 years because of competing risks. Our final cohort included 396,077 patients after applying inclusion and exclusion criteria.

Comorbidity, Socioeconomic, and Geographic Characteristics
The total number of medications dispensed within the previous year was used as a marker of comorbidity. The use of such measures has been validated as a comorbidity index and is described elsewhere. Socioeconomic status was defined as a binary variable (impoverished: yes or no). Any patient whose annual individual income was Can $15,500 or less (or who had a household income of Can $22,000 or less) and who applied for full subsidization for prescription drug dispensing fees was classified as impoverished. Patient residence was categorized as a binary term (urban vs rural) based on residential postal codes.

Derivation of the Baseline Risk Index
To disentangle baseline risk for future adverse events from the effects of other factors on mortality, we derived a baseline risk index using multiple logistic regression models that adjusted for various clinical characteristics but excluded age, sex, socioeconomic status, and location of residence. We modeled likelihood of death after 3 years of follow-up as a function of the following clinical variables: previous cardiovascular hospitalizations (stratified according to diagnosis), total number of previous cardiovascular hospitalizations, number of dispensed cardiovascular medications (excluding statins), and the comorbidity index. Similar risk-adjustment indexes have been previously used to characterize illness severity and validated in disease-specific cohorts (eg, acute myocardial infarction). The area under the receiver operating characteristic curve (AUROC) of our baseline risk index was...
0.71. When age and sex were added into the risk index, the AUROC increased to 0.79, suggesting good discriminat-
ing characteristics.

Statistical Analysis
We first compared demographic and clinical characteristics in patients with and without statin prescriptions. In un-
ivariate fashion, categorical variables were compared using χ² tests, and continuous variables were compared us-
ing either a t test or another nonpara-
meter test as appropriate.

We examined the relationship among baseline risk index, age, and statin pre-
scription using multiple logistic regres-
sion techniques, while adjusting for sex,
socioeconomic status, and rural vs ur-
ban status. We tested for multiple sta-
tistical interactions, including the in-
teraction between age and baseline risk,
in each of our models. Adjusted prob-
ability curves (ie, the probability of re-
ceiving vs not receiving statins) were
constructed according to age and the base-
line risk index by imputing average
covariate patterns for sex, income, and
geographic residence. When exam-
ing the probability of statin pre-
scription by age, we stratified the base-
line risk index into 3 groups (25th, 50th, and 75th percentiles of death). Similarly, when examining the prob-
ability of statin prescription by base-
line risk index, we categorized age into 3 subgroups (a typical 71-year-old, a
typical 75-year-old, and a typical
81-year-old).

A series of sensitivity analyses was per-
fomed to examine the robustness of our results. First, analyses were re-
peated by evaluating the prescription of all lipid-lowering therapies (eg, fi-
bic acid derivatives) rather than the
prescription of statins alone. Second, all
data were reanalyzed when confining the
cohort to patients with a history of
preexisting cardiovascular disease (ie,
excluding those with diabetes alone).
Third, due to potential concerns aris-
ing from the confounding “protec-
tive” survival effects of statins them-
selves, baseline risk was derived with
and without the inclusion of statins in
our risk-adjustment models. Fourth, we
undertook additional modifications to
the derivation of our risk-adjustment
index in which baseline risk was mod-
eled as a function of the composite of
death or myocardial infarction rather
than as a function of death alone. Fifth,
because of concerns that we might have
included patients with substantial co-
morbid conditions for which statins
might not be appropriate, we repeated
the analysis using 2 different cohorts.
One cohort excluded patients in the
75th percentile of the comorbidity in-
dex, and the other excluded patients
who died within 1 year of cohort in-
ception. Finally, we examined a differ-
ent risk index that excluded the com-
orbidity index and adjusted only for
(cardiovascular risks in both our origi-
nal cohort and lower risk cohorts. In
all of these sensitivity analyses, our
overall results did not materially
change. All statistical analyses were
performed using SAS statistical software,
version 8.2 (SAS Institute Inc, Cary,
NC). P<.05 was considered statisti-
cally significant for all analyses.

### Table 1. Baseline Participant Characteristics*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Statin Prescription (n = 75617)</th>
<th>No Statin Prescription (n = 320,406)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age, y</td>
<td>72.9 (5.0)</td>
<td>77.3 (7.4)</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>36,738 (48.6)</td>
<td>179,351 (56.0)</td>
</tr>
<tr>
<td>Low income, No. (%)</td>
<td>22,772 (30.1)</td>
<td>121,018 (37.8)</td>
</tr>
<tr>
<td>Rural residence, No. (%)*</td>
<td>11,029 (14.8)</td>
<td>58,181 (18.5)</td>
</tr>
<tr>
<td>Baseline risk index (mean adjusted probability of death within 3 years), %</td>
<td>21.1 (13.2)</td>
<td>27.5 (14.9)</td>
</tr>
<tr>
<td>Cardiovascular history, No. (%)</td>
<td>44,879 (59.3)</td>
<td>122,423 (38.2)</td>
</tr>
<tr>
<td>Hospitalization for angina</td>
<td>12,040 (15.9)</td>
<td>22,081 (6.9)</td>
</tr>
<tr>
<td>Hospitalization for AMI</td>
<td>22,706 (30.0)</td>
<td>154,247 (48.1)</td>
</tr>
<tr>
<td>Previous angiography</td>
<td>16,433 (21.7)</td>
<td>18,375 (5.7)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>37,866 (5.0)</td>
<td>3083 (9.6)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>7976 (10.5)</td>
<td>7041 (2.2)</td>
</tr>
<tr>
<td>Nitroglycerin use</td>
<td>41,238 (54.5)</td>
<td>114,350 (35.7)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>22,841 (30.2)</td>
<td>101,732 (31.8)</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>4820 (6.4)</td>
<td>30302 (9.5)</td>
</tr>
<tr>
<td>Carotid endarterectomy</td>
<td>1842 (2.4)</td>
<td>2731 (0.9)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>460 (0.6)</td>
<td>1728 (0.5)</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
<td>2471 (3.3)</td>
<td>8358 (2.6)</td>
</tr>
</tbody>
</table>

| Mean (SD) No. of cardiology visits per 100 patients within the previous year | 32.0 (46.7) | 15.5 (36.1) |
| Comorbidity index (mean [SD] No. of prescribed medications in the previous year) | 20.4 (17.6) | 15.4 (18.3) |
| Mean (SD) No. of total hospitalizations per 100 patients within the previous 5 years | 158 (20) | 160 (22) |

Abbreviations: AMI, acute myocardial infarction; CABG, coronary artery bypass graft surgery; CHF, congestive heart failure; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

*The determination of rural residence was based on 388,845 patients because of suppressed residential postal codes.

RESULTS

Baseline Characteristics

In our study sample, 271,504 patients (68.6%) had a history of cardiovas-
cular disease alone, 70,535 (17.8%) had diabetes mellitus alone, and 54,038
(13.6%) had both preexisting cardio-
vascular disease and diabetes mellitus. The median age of the overall cohort
was 75 years; 216,089 (54.6%) were women,
143,790 (36.3%) had low socioeco-
nomic status, and 69,210 (17.5%) lived
in rural areas (TABLE 1). The correla-
tion between age and the baseline risk
index was modest (r = 0.31). In this co-
hort, 75,617 patients (19.1%) were pre-
scribed statin therapy. Patients pre-
scribed statins were younger; were more
likely to be men; had a history of an-
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Please refer to the original document for the complete text.
tremes of illness severity but increased progressively and incrementally in patients with advancing age and advancing baseline risk. Furthermore, we observed a significant interaction effect between age and risk in the prescription of statin therapy. Thus, age and risk acted in concert to further reduce the propensity of physicians to prescribe statins in secondary prevention.

We do not believe that our findings are explainable by variations in affordability and/or accessibility of medications. Although patients in Ontario have to pay out of pocket for dispensing fees, the acquisition costs for statins are provided to all elderly patients free of charge. Moreover, our analyses also, to some extent, adjusted for baseline socioeconomic and geographic differences.

Statins are a useful medication to examine because of the substantial reductions in cardiovascular mortality and the lower adverse effect profiles compared with thrombolytic therapy or invasive cardiac procedures. The relationship between baseline risk and statin avoidance in secondary prevention patients likely reflects a systematic bias, which may be generalizable to other evidence-based therapies. Studies demonstrating the diminishing use of thrombolytics, cardiac catheterizations, and β-blockers in elderly patients in the setting of acute myocardial infarction may represent a similar phenomenon—an aversion to treat patients at high risk of future adverse events. The inverse relationship between baseline risk and treatment aggressiveness implies suboptimal evidence-based therapies when applied to real-world settings. To our knowledge, the treatment-risk paradox has not been demonstrated in a similar fashion. Other studies are needed to confirm our findings in different patient subsets using different therapies.

Several factors may explain the treatment-risk paradox for statins. First, physicians may have misconceptions about the benefit-harm tradeoffs. For example, physicians may feel reluctant to generalize clinical trial results to elderly patients with comorbidities on the grounds that such patients may experience fewer benefits and greater harm from the adverse effects of therapy. However, the relative survival benefits associated with statins appear to be consistent across multiple subgroups, including elderly patients. Furthermore, the impact of any therapy in the population depends on baseline risk more than relative efficacy. Although the absolute rate of serious harmful adverse effects may be increased for patients at highest baseline risk compared with their healthier counterparts, the rate of life-threatening complications required to negate potential survival benefits from treatment rarely approaches the incidence encountered in real-world settings, especially for statins, where the rate of severe complications is extremely low. This overemphasis of harm combined with an underappreciation of benefits may favor a more conservative hands-off approach to treatment.

Second, physicians may prejudge the compliance of their patients and be less inclined to prescribe therapies to patients thought unlikely to adhere to treatment. Patients at higher baseline risk may not perceive the benefits of additional therapy and have an increasing unwillingness to be receptive to physicians’ recommendations. Indeed, factors that contribute to poor compliance in elderly patients include cognitive, functional, and social decline—all factors associated with higher baseline risk of adverse cardiac events. However, preconceived atti-

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**Figure.** Relationship of Adjusted Probability of Receiving Statins With Baseline Risk According to Age and Age According to Baseline Risk

The 95% confidence intervals were very small in the probability estimations of statin use across the whole spectrum of baseline risk and age (data not shown). A, Younger age is 71 years, median age is 75 years, and older age is 81 years. Baseline risk refers to the expected probability of death in 3 years as derived at inception. \( P<.001 \) for the probability of statin prescription for variations in age, risk, and age-risk interaction. B, Low risk is the 25th percentile for the expected probability of death in 3 years as derived at inception, median risk is the 50th percentile, and high risk is the 75th percentile. \( P<.001 \) for the probability of statin prescription for variations in age, risk, and age-risk interaction.
tudes toward compliance may too be misguided, given the evidence suggesting improved compliance rates of statins among elderly patients with higher severity of cardiac illness. Therefore, it is important for physicians to address the diverse needs of elderly patients and emphasize therapies that would derive substantial benefits to promote adherence.

Finally, the treatment-risk paradox may be explained by physician inattentiveness to cardiovascular prevention, especially when multiple conditions co-exist. For example, available evidence suggests that clinicians who care for patients with chronic diseases become less attentive when managing the necessities of other concurrent conditions due to constraints in time, expertise, and preferences. Several limitations of our study merit consideration. First, we did not have access to individual cholesterol levels, and it is not possible to determine the appropriateness of statin prescription on an individual basis. Since all patients in our cohort were eligible for secondary prevention, we believe that most of our cohort would have qualified for and derived substantial benefits from statin therapy. Furthermore, patients eligible for statins are likely equally distributed across the risk spectrum, and thus, our observed treatment pattern across the age-risk spectrum is unlikely to be affected. Second, patients' risk profiles characterized by administrative data may be subject to undercoding of comorbidity. Therefore, we designed our cohort to include patients with a prior history of cardiovascular disease or diabetes to maximize specificity. Third, we used all-cause mortality as our main determinant of baseline risk. Although admitted, the benefits of statins are largely mediated through their effects on cardiovascular outcomes, randomized trials have demonstrated that statins exert consistent reductions in all-cause mortality. Moreover, studies have found that the determination of cardiac death may be inaccurate and could potentially lead to misinterpretation of data. Finally, our data reflected prescribing patterns approximately 5 years ago, and overall utilization rates of statins have likely increased in the interim. However, given the magnitude of discordance between baseline risk and treatment propensity observed in this study, it is unlikely that the treatment-risk paradox will cease to exist.

In conclusion, we demonstrate that physician aggressiveness in the prescription of statin therapy to elderly patients for secondary prevention in Ontario was inversely correlated with baseline cardiovascular risk independent of age. The treatment-risk paradox phenomenon was not only applicable at the extremes of illness severity but was also observed throughout the entire spectrum of illness severity. Given the importance of baseline risk in determining the impact of therapy in the population, the treatment-risk paradox implies that the survival benefits of statin therapy may never be fully realized until physicians appropriately tune their prescribing behaviors to the risk profiles of their patients.

Author Contributions: All 3 authors of the study had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors had complete independence in the collection, analysis, and interpretation of the study results.

Study concept and design: Ko, Mamdani, Alter.

Acquisition of data: Mamdani, Alter.

Analysis and interpretation of data: Ko, Alter.

Drafting of the manuscript: Ko, Alter.

Critical revision of the manuscript for important intellectual content: Ko, Mamdani, Alter.

Statistical expertise: Ko, Mamdani, Alter.

Obtained funding: Mamdani, Alter.

Supervision: Alter.

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It is no good to try to stop knowledge from going forward. Ignorance is never better than knowledge.
—Enrico Fermi (1901-1954)