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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Statins for secondary prevention provide a useful test case for several reasons. First, statins are among the most efficacious therapies in reducing future cardiac events and mortality.9,10 Initially shown to be beneficial in patients with substantially elevated cholesterol,9,10 the benefits of statin therapy have currently extended to previously “normal” cholesterol levels.11-14 Second, clinical trials have demonstrated consistent treatment effects across multiple subgroups, including elderly persons.15 Third, clinical guideline recom-
tients and baseline risk throughout the prescription of statins among a second-
tarily aggressive in the association between physician aggressiveness in the
prescription of statins among a secondary prevention cohort of elderly pa-
ents 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 administra-
tive databases with follow-up tracking of mortality over time, regardless of location of death. Briefly, GOLD in-
cludes 1.44 million residents aged 66 years or older who were alive in Ontario on April 1, 1998. Unique en-
crypted patient identifiers were used for linkage in the multiple databases to pro-
tect patient confidentiality. We identi-
ified previous hospitalizations using the Canadian Institute of Health Informa-
tion hospital discharge abstracts and identified physician visits and previous cardiac interventions using physi-
cian claims data obtained by the On-
tario Health Insurance Plan. We used the ODB to obtain information on medi-
cation prescriptions within 1 year be-
fore cohort inception. Demographic and geographic information was identified using the Registered Persons Database and data from the official 1996 Cen-
sus. We excluded all non-Ontario resi-
dents and those who did not have a valid health card number. The re-
search ethics board of Sunnybrook and Women's College Health Science Cen-
ter, University of Toronto, approved the study and waived a requirement for in-
formed consent.

Study Cohort
We selected patients at high risk of fu-
ture cardiovascular events and in-
cluded patients older than 66 years with a history of cardiovascular disease or dia-
abetes mellitus while undergoing medi-
tal therapy. We defined a statin pre-
scription as one in which a patient had been dispensed any prescription for
statin medication within the year be-
fore the inception of the cohort. Statins covered in the ODB at the time of the
study included atorvastatin, cerivast-
tatin, fluvastatin, lovastatin, pravast-
tin, and simvastatin. We defined cardio-
vascular disease in the study sample as 1 or more of the following: cardiovas-
cular hospitalization within 5 years, coronary intervention (cardiac catheter-
ization, percutaneous coronary inter-
vention, or coronary artery bypass graft surgery) within 5 years, or angina (de-
fined as concurrent use of nitrates within
the year of cohort inception). Using hos-
pital discharge abstracts, a previous cardio-
vascular hospitalization was de-

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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 univari-ate fashion, categorical variables were compared using \( \chi^2 \) tests, and con-
tinuous variables were compared using either a \( t \) test or another nonpara-
metric test as appropriate.

We examined the relationship among baseline risk index, age, and statin pre-
scription using multiple logistic regression techniques, while adjusting for sex, socioeconomic status, and rural vs ur-
ban status. We tested for multiple sta-
tistical interactions, including the inter-
action 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 baseline risk index by imputing aver-
age covariate patterns for sex, income, and geographic residence. When ex-
amining 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 performed to examine the robustness of our results. First, analyses were re-
peated by evaluating the prescription of all lipid-lowering therapies (eg, fi-
bric 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 arising 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-
ed 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 co-
morbidity 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 per-
formed using SAS statistical software, version 8.2 (SAS Institute Inc, Cary, NC). \( P<.05 \) was considered statistically significant for all analyses.

### RESULTS

#### Baseline Characteristics

In our study sample, 271 504 patients (68.6%) had a history of cardiovascular disease alone, 70 535 (17.8%) had diabetes mellitus alone, and 54 038 (13.6%) had both preexisting cardio-
vase 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 socioeconomic 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-

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Statin Prescription (n = 75 617)</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>Hospitalization for angina</td>
<td>44 879 (59.3)</td>
</tr>
<tr>
<td>Hospitalization for AMI</td>
<td>12 040 (15.9)</td>
<td>22 081 (6.9)</td>
</tr>
<tr>
<td>Hospitalization for CHF</td>
<td>22 706 (30.0)</td>
<td>154 247 (48.1)</td>
</tr>
</tbody>
</table>
| Previous angio
graphy | 16 433 (21.7) | 18 375 (5.7) |
| Previous PCI | 3786 (5.0) | 3083 (0.96) |
| Previous CABG | 7976 (10.5) | 7041 (2.2) |
| Nitroglycerin use | 41 238 (54.5) | 114 350 (35.7) |
| Diabetes mellitus | 22 841 (30.2) | 101 732 (31.8) |
| Stroke/TIA | 4820 (6.4) | 30 302 (9.5) |
| Carotid endarterectomy | 1842 (2.4) | 2731 (0.9) |
| Abdominal aortic aneurysm | 1842 (2.4) | 2731 (0.9) |
| Mean (SD) hospitalizations per 100 patients within the previous year | 30.2 (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.
gin, acute myocardial infarction, or prior cardiac invasive procedures; and had more visits to a cardiologist within the past year. Conversely, patients not prescribed statins were more likely to have diabetes, congestive heart failure, or stroke; to have lower socioeconomic status; and to live in rural areas (P<.001 for all) (Table 1). Table 2 illustrates the observed rates of death and the expected probabilities of death at 3 years according to different categories of age and different categories of the baseline risk index.

**Relationship Between Baseline Risk and Statin Prescription**

Table 3 illustrates the independent determinants of statin prescription according to multivariable analysis. Both age and baseline risk inversely correlated with the likelihood of receiving statins, after adjusting for sex, socioeconomic status, and rural vs urban residence. Moreover, age interacted with baseline risk in determining statin prescription (P<.001 for the interaction term). For each year of increase in age and each 1% increase in the baseline risk index, there was a 6.4% lower odds of statin prescription (adjusted odds ratio, 0.94; 95% confidence interval, 0.93-0.95; P<.001) after adjusting for all other factors.

Progressively lower use of statins in patients with higher cardiovascular risk existed across the full spectrum of cardiovascular risk (Figure, A). Similarly, we also observed lower use of statins in elderly patients across the entire spectrum of age (Figure, B). 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).

**COMMENT**

Despite convincing evidence demonstrating substantial mortality reductions from the use of statins in secondary prevention, we found that only a small proportion of elderly patients with preexisting cardiovascular disease were prescribed statin therapy in Ontario. Moreover, the likelihood that physicians prescribed statin therapy was inversely correlated with baseline risk and did so across the entire spectrum of illness severity, independent of age. Finally, the effects of age and baseline risk had a synergistic effect on the prescribing behaviors of physicians.

Our observed low prescription rate of statin therapy adds to a growing body of literature demonstrating that statin therapy is substantially underused. This is concordant with recent data collected by the National Registry of Myocardial Infarction, in which only 31.7% of all patients discharged from the hospital with acute myocardial infarction were prescribed lipid-lowering therapy. Furthermore, when examining treatment targets, a recent survey demonstrated that only 5.4% of patients known to have hyperlipidemia had achieved a target total cholesterol level in the United States, representing a substantial opportunity for improvement.

Although the overall prescription of statins in the population was low, we found that the decision to withhold therapy was not only observed at the ex-

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**Table 2. Observed and Expected Probability of 3-Year Mortality in Ontario According to Age and Baseline Risk**

<table>
<thead>
<tr>
<th></th>
<th>Aged 66-74 Years</th>
<th>Aged 75-80 Years</th>
<th>Aged ≥81 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>59,885</td>
<td>90,168</td>
<td>28,061</td>
</tr>
<tr>
<td>Observed mortality at 3 years, %</td>
<td>7.8</td>
<td>12.8</td>
<td>34.4</td>
</tr>
<tr>
<td>Expected probability of 3-year mortality at baseline, % (95% CI)†</td>
<td>8.9 (8.7-9.2)</td>
<td>15.0 (14.7-15.3)</td>
<td>38.8 (38.2-39.4)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.
*Adjusted probability of death incorporated multiple logistic regression and was adjusted for sex, low vs average income level, rural-urban status, and the interaction between age and baseline risk categories. Baseline risk is derived from the baseline risk index (probability of death at 3 years from inception) and subdivided into quartiles. Low indicates lowest risk quartile; intermediate, interquartile range; and high, highest risk quartile.
†P<.001 for the test for trend across age categories within each baseline risk category using the weighted Mantel-Haenszel χ² test for trend (weighted for sample size).

**Table 3. Adjusted Probability of Statin Prescription in Ontario According to Age and Baseline Risk**

<table>
<thead>
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<td>No. of patients</td>
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</tr>
<tr>
<td>Adjusted probability of statin prescription, % (95% CI)†</td>
<td>37.7 (37.3-38.2)</td>
<td>26.7 (26.4-27.1)</td>
<td>23.4 (22.8-23.9)</td>
</tr>
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Abbreviation: CI, confidence interval.
*Adjusted probability of statin prescription incorporated multiple logistic regression and was adjusted for sex, low vs average income level, rural-urban status, and the interaction between age and baseline risk categories. Baseline risk is derived from the baseline risk index (probability of death at 3 years from inception) and subdivided into quartiles. Low indicates lowest risk quartile; intermediate, interquartile range; and high, highest risk quartile.
†P<.001 for the test for trend across age categories within each baseline risk category using the weighted Mantel-Haenszel χ² test for trend (weighted for sample size).
minimizing the use of thrombolytics, cardiac catheterizations, and β-blockers in elderly patients in the setting of acute myocardial infarction. Furthermore, patients at high risk of future adverse events. The inverse relationship between baseline risk and treatment aggressiveness implies suboptimal benefits of 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-

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. Baseline risk refers to the expected probability of death in 3 years as derived at inception. Accurate 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. Accurate for the probability of statin prescription for variations in age, risk, and age-risk interaction.

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tudes toward compliance may be misguided, given the evidence suggesting improved compliance rates of statins among elderly patients with higher severity of cardiac illness.32 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 inattention to cardiovascular prevention, especially when multiple conditions coexist. 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.8

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 admittedly, 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, studies33,34 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.35,36 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 attending their prescribing behaviors to the risk profiles of their patients.

REFERENCES

34. Gottlieb SS. Dead is dead: artificial definitions are no substitute. Lancet. 1997;349:662-663.

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