Relationship Between Adherence to Evidence-Based Pharmacotherapy and Long-term Mortality After Acute Myocardial Infarction

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CLINICAL TRIALS HAVE DEMONSTRATED THAT SELECTED PHARMACOTHERAPIES REDUCE CARDIOVASCULAR MORTALITY.1,2 HOWEVER, THEIR PROJECTED SURVIVAL IMPACT IN THE REAL WORLD IS LESS KNOWN, IN PART BECAUSE OF VARIATIONS IN DRUG ADHERENCE.3,4 ALTHOUGH IT IS KNOWN THAT ADHERENCE TO EVIDENCE-BASED PHARMACOTHERAPY PREDICTS BETTER SURVIVAL,3,4 NO POPULATION OUTCOME STUDY HAS ATTEMPTED TO DIFFERENTIATE WHETHER THESE ASSOCIATIONS ARE ATTRIBUTABLE TO THE DRUG'S BIOLOGICAL RESPONSIVENESS (HEREIN TERMED DRUG EFFECT) OR TO THE ADOPTION OF HEALTHIER LIFESTYLES THAT OFTEN ACCOMPANY ADHERENT BEHAVIORS (HEREIN TERMED HEALTHY ADHERER EFFECT). IF MORTALITY GAINS ARE DIRECTLY ATTRIBUTABLE TO BIOLOGICAL RESPONSIVENESS, THEN ONE MIGHT HYPOTHESIZE THAT OUTCOME BENEFITS CORRELATE WITH ADHERENCE INTENSITY AND THAT SURVIVAL-ADHERENCE GAINS FOLLOW A “DOSE-RESPONSE”-TYPE GRADIENT. IF CONFIRMED, INTERVENTIONS THAT SELECTIVELY TARGET AND IMPROVE DRUG-TAKING BEHAVIORS SHOULD TRANSFORM INTO IMPORTANT MORTALITY ADVANTAGES WHEN APPLIED TO REAL-WORLD POPULATIONS.

The objective of our study was to examine the relationship between drug adherence and mortality following acute myocardial infarction (AMI) in a large cohort from Ontario. Our study focuses on seniors aged 65 years or older for several reasons. First, elderly populations represent a vulnerable group with high baseline cardiovascular risk and a propensity for premature drug discontinuation due to complexities in medical regimens, tolerance, and concerns about harmful adverse effects.12 Second, with the exception of modest co-payment dispensing fees, in Canada...
cardiovascular medications are free of charge for patients aged 65 years or older. Therefore, affordability factors should not significantly affect adherence propensities. Third, administrative data allows for the tracking, monitoring, and surveillance of all medication prescriptions in Ontario. Consequently, adherence rates as measured using prescription refill data can be determined with precision. To help evaluate whether the association between adherence and mortality (if present) was more attributable to drug effects rather than to healthy adherer effects, we examined 3 medication classes, 2 of which are associated with proven mortality benefits (statins and β-blockers), the third medication class (calcium channel blockers) was examined as a control given the absence of documented post–myocardial infarction survival advantages. This study was approved (and informed consent was waived) by the research ethics boards of Sunnybrook Health Science Center.

METHODS

Sources of Data

We obtained information from the Ontario Myocardial Infarction Database, which draws together data from a variety of administrative sources. Hospital discharge abstracts compiled by the Canadian Institute for Health Information yielded information pertaining to the index admission, demographic characteristics, coexisting illnesses, use of in-hospital procedures, and mortality. Data on claims for payment for physicians’ services from the Ontario Health Insurance Plan and Canadian Institute for Health Information hospital discharge data were used to determine rates of use of cardiac procedures. The Ontario Registered Persons Database provided data on mortality over time, regardless of where death occurred (limited to Ontario). Drug use was determined using the Ontario Drug Benefit prescription claims database, which contains information on outpatient prescription drug use and costs for all 1.4 million residents aged 65 years or older in Ontario. Residents may fill prescriptions at any pharmacy within Ontario and have a co-payment of a maximum of Can $6.11 with each prescription after a Can $100 deductible. Senior residents with low income (single seniors with income of less than Can $16 018 and senior couples with less than Can $24 175 per year) have a co-payment of a maximum of Can $2 and no deductible.14

Patient Population

The cohort consisted of patients aged 66 years or older, surviving at least 1 year and 3 months after hospitalization with a most responsible diagnosis of AMI between April 1, 1999, and May 1, 2003, a sufficiently long and stable enough period to allow for the provision and dispensing of drugs and the adherence associated with medication use following hospital discharge after AMI.6 The accuracy of AMI coding has been validated through multi-center chart audits.17 We excluded any patient who had been hospitalized with an AMI in the year before the index admission because we wanted to reduce the chance that subgroups within the cohort varied in terms of severity of cardiovascular disease.

All patients had to fill at least 1 of 3 possible drug prescriptions (for statins, β-blockers, or calcium channel blockers) within 3 months of AMI hospital discharge. Both statins and β-blockers are recommended in secondary prevention after MI (class 1 level of evidence), whereas calcium channel blockers are not recommended as a first-choice drug in secondary prevention (class 2 level of evidence).8,10

Assessment of Adherence

Data on the quantity dispensed and number of days supplied from each filled prescription were used to calculate the proportion of days on which a patient had pills available in the year following the first filled prescription after discharge (proportion of days covered [PDC]). We determined adherence for a uniform period of 1 year for all patients to ensure equal and accurate long-term adherence behavior profiles. The use of short-term adherence time intervals (ie, ≤6 months) to characterize PDC did not reflect long-term adherence behavior as accurately as the use of 1-year adherence time intervals (eg, area under the receiver operating characteristic curves for statins and β-blockers were 0.75-0.79 vs 0.84-0.93 when using 6-month vs 1-year exposure periods, respectively). Patients were subdivided a priori into 3 categories according to PDC: high adherence (PDC ≥80%), intermediate adherence (PDC of 40%-79%), and low adherence (PDC <40%).6

Disease Severity and Comorbidity

To control for severity of illness on admission, we used the Ontario AMI mortality prediction rule for 30-day and 1-year mortality, which included the variables of age, sex, severity of cardiac disease (eg, congestive heart failure, cardiogenic shock, and arrhythmia), and presence or absence of coexisting illnesses (eg, diabetes mellitus, stroke, cancer, and acute or chronic renal disease).20 The prediction rule, which was derived and validated in a different population than the current one,20 has demonstrated good accuracy (ie, areas under the receiver operating characteristic curve of 0.78 for 30-day mortality and 0.79 for 1-year mortality). To adjust for interval changes in disease status during the 1-year and 3-month adherence assessment period beginning at AMI hospital discharge, we identified whether patients received revascularization procedures (coronary artery bypass graft surgery or percutaneous coronary intervention), were admitted to the hospital because of ischemic heart disease (International Statistical Classification of Diseases, 10th Revision [ICD-10] codes 120-125), cancer (codes C00-C99), metabolic diseases (codes E00-E90), mental disorders (codes F00-F99), stroke (codes I60-I69), diseases of the respiratory system (codes J00-J99), and the number of admissions for all conditions during this period. Furthermore, we adjusted
for concomitant use of other cardiac medications (angiotensin-converting enzyme inhibitors, statins, β-blockers, and calcium channel blockers) where applicable.

**Mortality**

Long-term mortality was our primary outcome measure and was assessed until the last available follow-up date of August 1, 2005 (a median of 2.4 years of follow-up). Patients were censored if they reached the end of the observation period.

**Statistical Analysis**

To analyze differences in baseline characteristics across adherence levels, we tested for linear trends using a Mantel-Haenszel $\chi^2$ test for trend (categorical variables) or linear regression models (continuous variables), where appropriate. Multivariable logistic regression models, adjusting for all baseline factors, were constructed to examine predictors of adherence to statins, β-blockers, and calcium chan-

| Table 1. Characteristics of Patients According to 1-Year Adherence to Statins, β-Blockers, and Calcium Channel Blockers* |
|-------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|
| Adherence Level†        | Statins                | β-Blockers             | Calcium Channel Blockers |
| Characteristics         | High (N=1196)          | Intermediate (N=2476)  | Low (N=2602)            | High (N=1780)          | Intermediate (N=4267)  | Low (N=2164)            |
| Patients                | 14.34±5.0†             | 24.0±7.5               | 10.1±7.0                | 17.8±9.0               | 42.7±6.5               | 21.4±6.5                |
| Age, mean (SD), y       | 74.4±6.0†              | 74.3±6.0               | 76.5±6.0                | 75.8±6.0               | 75.7±6.0               | 76.5±6.0                |
| Women                   | 5910                   | 1049                   | 515.9                  | 8112                   | 1766                   | 894.1                  |
| Low income              | 4032                   | 676                    | 361.9                  | 5378                   | 1196                   | 658.0                  |
| Specialty of attending physician |            |                      |                        |                        |                        |                        |
| Cardiology              | 74.7±4.0†              | 1237                   | 525.9                  | 8630                   | 2096                   | 1019.9                 |
| General practice        | 2496                   | 390                    | 199.9                  | 3502                   | 815                    | 472.9                  |
| Internal medicine       | 2396                   | 440                    | 179.9                  | 3109                   | 780                    | 370.9                  |
| Other                   | 1984                   | 337                    | 188.9                  | 2627                   | 506                    | 303.9                  |
| Drug therapy            | Prior use of study drug‡ | 5881                   | 1059                   | 246.9                  | 6468                   | 1518.9                 |
| Concomitant statins§    | NA                     | 11.150                 | 2602                   | 1160                   | 1780                   | 1019.9                 |
| Concomitant β-blockers§ | 12.064                 | 1976                   | 861.9                  | NA                     | 4154                   | 943.9                  |
| Concomitant calcium channel blockers§ | 4203 | 722                    | 300.4                  | 4538                   | 1080                   | 673.9                  |
| Concomitant angiotensin-converting enzyme inhibitors§ | 11.246 | 1853                   | 810.0                  | 13.526                 | 3181                   | 1580.0                 |
| Comorbidity at index AMI | Shock                 | 86.8                   | 14.8                   | 5.3                   | 125.9                   | 21.9                   |
| Pulmonary edema         | 143.5                  | 29.4                   | 13.4                   | 179.4                  | 43.4                   | 30.4                   |
| Congestive heart failure| 2812.9                 | 474.5                  | 252.6                  | 3861.7                 | 879.5                  | 441.5                  |
| Cardiac dysrhythmia     | 2267.5                 | 361.5                  | 177.5                  | 2985.6                 | 733.5                  | 415.5                  |
| Cerebrovascular disease | 502.5                  | 75.5                   | 44.5                   | 625.5                  | 137.5                  | 78.5                   |
| Diabetes with complications | 488.5                 | 96.5                   | 47.5                   | 590.5                  | 146.5                  | 71.5                   |
| Acute renal failure     | 287.5                  | 48.5                   | 24.5                   | 357.5                  | 90.5                   | 35.5                   |
| Chronic renal failure   | 545.5                  | 120.5                  | 54.5                   | 679.5                  | 201.5                  | 80.5                   |
| Cancer                  | 215.5                  | 36.5                   | 16.5                   | 304.5                  | 86.5                   | 39.5                   |

*Continued*
calcium channel blockers separately. The univar-
iable relationship between adherence and mortal-
ty was examined separately for each drug using Kaplan-Meier plots and the log-rank test. Cox propor-
tional hazards models were con-
structed by standard statistical tests on propor-
tionality to adjust for age, sex,
 socioeconomic status (using a “low-
income” variable, based on patient
taxation data, which excluded patients from co-payment dispensing fees), year of admission, specialty of attend-
ing physician, severity of illness, inter-
current hospitalizations during the 1-year and 3-month adherence assessment
period, use of respective drug within 6 months prior to admission, concomitant use of angiotensin-
converting enzyme inhibitors, and, where applicable, statins, β-blockers, and calcium channel antagonists. The propor-
tional hazards assumption was not violated. All statistical models accounted for the clustering of patients within admitting hospitals using the robust sandwich estimate of Lin and Wei.

Multiple sensitivity analyses were per-
formed, including a propensity analysis in which patients were strati-
fied into quintiles according to the predicted probability of adherence level con-
tional on the baseline covari-
ates. The overall relationship between adherence and mortality was obtained by combining the estimates across quin-
tiles. Statistical significance was de-

defined as a 2-tailed \( P < .05 \). All analyses were performed using SAS software, version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS
There were 47,681 patients admitted with AMI and 31,455 patients who sur-
vived for at least 1 year and 3 months. Of these, 17,823 (37%) filled a prescription for a statin, 24,319 (77%) for a β-blocker, and 9,168 (30%) for a calcium channel blocker within 3 months of discharge.

Determinants of Adherence
The mean 1-year adherence rates, as de-
termined by the PDC, were 87.5% (SD, 20.5%) for statins, 83.9 (SD, 24%) for β-blockers, and 78.9 (SD, 28.8%) for calcium channel blockers. The propor-
tion of patients quitting drug treat-
ment altogether within the first year (defined as a 1-year PDC < 10%) was uniformly low for all drugs (1.1% for statins, 1.7% for β-blockers, and 3.2% for calcium channel blockers). However, 13.2%, 19.6%, and 33.5% of patients permanently discontinued their statins, β-blockers, and calcium channel blockers, respectively, at some point during the entire median 2.4-year ob-
server follow-up period (perma-
nent discontinuation was defined as the absence of an expected refill prescrip-
tion based on the number of previous pills dispensed, assessed over an interval of ≥6 months from the preceding prescription).

Table 1 illustrates the relationship be-
tween baseline patient characteristics.
and drug adherence. After adjustment for baseline factors (Table 2), increasing age, psychiatric illnesses, and increasing numbers of recurrent admissions within the year following AMI remained as independent determinants of poorer adherence to both statins and β-blockers (P<.001). Prior evidence-based medication use within 6 months preceding the index AMI hospitalization was associated with improved adherence to these therapies (P<.001). Post-MI revascularization was associated with improved adherence to statins but higher discontinuation rates of β-blockers and calcium channel blockers, which may have been partially attributable to lower symptom burden among those who had successful revascularization.

**Mortality**

**Figure 1** illustrates that the unadjusted relationship between adherence and mortality followed a dose-response-type adherence-mortality gradient for statins and β-blockers.

### Table 2. Multivariable Analysis of the Association of Patient Characteristics With 1-Year Adherence Level

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Statins</th>
<th>β-Blockers</th>
<th>Calcium Channel Blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% Confidence Interval)</td>
<td>Odds Ratio (95% Confidence Interval)</td>
<td>Odds Ratio (95% Confidence Interval)</td>
</tr>
<tr>
<td>Age (for each additional year)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.00 (0.99–1.01)</td>
<td>1.03 (1.02–1.04)</td>
<td>1.00 (1.00–1.01)</td>
</tr>
<tr>
<td>Year of AMI (for each additional year)</td>
<td>1.04 (1.00–1.08)</td>
<td>1.05 (1.00–1.11)</td>
<td>0.95 (0.92–0.98)</td>
</tr>
<tr>
<td>Low income</td>
<td>0.95 (0.96–1.05)</td>
<td>1.08 (0.94–1.24)</td>
<td>0.91 (0.84–0.99)</td>
</tr>
<tr>
<td>Specialty of attending physician</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiology</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>General practice</td>
<td>0.91 (0.81–1.03)</td>
<td>1.04 (0.87–1.23)</td>
<td>0.96 (0.87–1.05)</td>
</tr>
<tr>
<td>Internal medicine</td>
<td>1.10 (0.98–1.24)</td>
<td>0.97 (0.81–1.16)</td>
<td>1.03 (0.91–1.13)</td>
</tr>
<tr>
<td>Other</td>
<td>0.98 (0.96–1.11)</td>
<td>1.08 (0.90–1.30)</td>
<td>0.95 (0.85–1.05)</td>
</tr>
<tr>
<td>Drug therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior use of drug‡</td>
<td>1.10 (1.01–1.21)</td>
<td>0.40 (0.34–0.46)</td>
<td>0.93 (0.86–1.00)</td>
</tr>
<tr>
<td>Concomitant statin‡</td>
<td>NA</td>
<td>NA</td>
<td>0.94 (0.85–1.02)</td>
</tr>
<tr>
<td>Concomitant β-blocker†</td>
<td>0.88 (0.78–0.99)</td>
<td>0.78 (0.66–0.92)</td>
<td>0.91 (0.81–1.03)</td>
</tr>
<tr>
<td>Concomitant calcium channel blocker‡</td>
<td>0.93 (0.85–1.03)</td>
<td>0.88 (0.76–1.02)</td>
<td>1.14 (1.00–1.31)</td>
</tr>
<tr>
<td>Comorbidity at index AMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shock</td>
<td>0.98 (0.96–1.10)</td>
<td>0.46 (0.14–1.46)</td>
<td>0.89 (0.43–1.11)</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>1.18 (0.79–1.78)</td>
<td>1.24 (0.69–2.22)</td>
<td>0.93 (0.66–1.30)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0.91 (0.81–1.25)</td>
<td>1.07 (0.91–1.25)</td>
<td>0.95 (0.88–1.05)</td>
</tr>
<tr>
<td>Cardiac dysrhythmia</td>
<td>0.93 (0.83–1.05)</td>
<td>0.96 (0.81–1.14)</td>
<td>1.08 (0.99–1.18)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>0.83 (0.65–1.07)</td>
<td>1.13 (0.82–1.57)</td>
<td>0.89 (0.74–1.08)</td>
</tr>
<tr>
<td>Diabetes with complications</td>
<td>1.02 (0.81–1.30)</td>
<td>1.21 (0.87–1.68)</td>
<td>0.94 (0.77–1.14)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>0.87 (0.64–1.20)</td>
<td>0.84 (0.54–1.30)</td>
<td>1.01 (0.80–1.29)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>1.20 (0.96–1.49)</td>
<td>1.09 (0.81–1.50)</td>
<td>1.19 (1.00–1.42)</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.92 (0.84–1.03)</td>
<td>0.81 (0.70–0.95)</td>
<td>0.92 (0.85–1.00)</td>
</tr>
<tr>
<td>Readmission within 1 y of discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revascularization</td>
<td>0.97 (0.89–1.07)</td>
<td>0.60 (0.51–0.70)</td>
<td>1.26 (1.17–1.36)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1.08 (0.96–1.23)</td>
<td>1.05 (0.88–1.26)</td>
<td>1.05 (0.96–1.16)</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.47 (1.06–2.04)</td>
<td>1.06 (0.62–1.79)</td>
<td>1.15 (0.88–1.53)</td>
</tr>
<tr>
<td>Psychiatric illness</td>
<td>1.65 (1.00–2.70)</td>
<td>3.28 (0.70–5.49)</td>
<td>1.48 (1.05–2.08)</td>
</tr>
<tr>
<td>Endocrine illness</td>
<td>1.42 (1.02–1.97)</td>
<td>1.50 (0.98–2.30)</td>
<td>1.12 (0.86–1.44)</td>
</tr>
<tr>
<td>Apoplexia</td>
<td>1.51 (1.00–2.06)</td>
<td>1.39 (0.90–2.15)</td>
<td>1.26 (0.99–1.61)</td>
</tr>
<tr>
<td>Respiratory illness</td>
<td>1.22 (0.98–1.52)</td>
<td>1.19 (0.89–1.60)</td>
<td>1.11 (0.93–1.33)</td>
</tr>
</tbody>
</table>

Abbreviations: AMI, acute myocardial infarction; NA, not applicable.

*High adherence was defined as proportion of days covered (PDC) of 80% or more; intermediate adherence, PDC of 40% to 79%; and low adherence, PDC of less than 40%.

†Claim of drug within 90 days of discharge.

‡Use of respective drug analyzed within 6 months prior to index AMI.

§For each additional admission for any condition within the year after discharge.

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However, there was no such adherence-mortality association with calcium channel blockers. After adjustment for baseline patient characteristics, compared with those with high levels of adherence to statins (PDC ≥80%), the risk of mortality was 12% higher among patients with intermediate (PDC of 40%-79%) adherence (adjusted hazard ratio, 1.12; 95% confidence interval, 1.01-1.25; P = .03) and was 25% higher among patients with poor (PDC <40%) adherence (adjusted hazard ratio, 1.25; 95% confidence interval, 1.09-1.42; P = .001) (Table 3). While the directional association between adherence and mortality was similar to statins for β-blockers, the magnitude of association between adherence and mortality was smaller with β-blockers. There was no relationship between calcium channel blocker adherence and mortality (Table 3), regardless of whether calcium channel blockers were classified as dihydropyridines or nondihydropyridines.

### Sensitivity Analysis

Several sensitivity analyses were performed. First, to ensure that our findings were applicable to longer-term adherence (ie, as assessed beyond 1 year), we reanalyzed our data and evaluated whether longer-term adherence assessment intervals, as assessed over 3-year periods, generated similar relationships to mortality as our primary analysis. Our results did not change appreciably.

Second, to ensure that our method did not introduce survival bias, we reestimated the adherence-mortality relationship among those surviving at least 3 months (the shortest possible survival window to fill a first prescription) and found similar adherence-mortality associations to those determined in our primary analysis, in which patients were required to survive until 15 months.

Third, we stratified the population into prespecified subgroups according to predicted 30-day mortality tertiles to ensure that any adherence-mortality relationship also applied to various risk groups. While adherence-mortality associations did not always achieve statistical significance across all risk groups because of sample size, subgroup analyses yielded trends similar to those seen in our primary analyses (FIGURE 2).

Fourth, to help further disentangle biological drug effects from healthy adherer effects, we evaluated the impact of cardiovascular drug adherence on a sample of prespecified outcomes in which neither clinical evidence nor biological plausibility exits. These outcomes were the 3 most prevalent malignancies in North America, which have all been found to be associated in part with lifestyle behaviors, hospitalizations for lung cancer (ICD-10 codes C33–C34; n = 245 in the current study), breast cancer (ICD-10 code C50 [women only]; n = 91), and prostate cancer (ICD-10 code C61 [men only]; n = 206). As expected, no significant relationships were seen between drug adherence and subsequent risk of lung cancer (test for trend: P = .37, P = .98, and P = .86 for statins, β-blockers, and calcium channel blockers, respectively), breast cancer (test for trend: P = .54, P = .95, and P = .98, respectively), or prostate cancer (test for trend: P = .45, P = .90, and P = .75, respectively).

Finally, the use of propensity-based methods to compare adherence-mortality associations generated virtually identical findings to those which relied on standard modeling.  

### COMMENT

In this large, population-based cohort study, we demonstrated a positive relationship between adherence to evidence-based pharmacotherapy and survival following AMI. Specifically, for statins and β-blockers, adherence correlated positively with survival in a graded dose-response-type fashion. Conversely, no such adherence-mortality relationship existed for calcium channel blockers, a

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**Figure 1.** Kaplan-Meier Estimates of Time to Death for Statin, β-Blocker, and Calcium Channel Blocker Users According to Adherence Level
Although other studies have demonstrated lower mortality among patients with higher adherence levels, most studies have been confined to clinical trial populations. By comparison, fewer studies have evaluated whether an adherence-mortality gradient exists among real-world populations. One such exception involved a recent study examining the mortality effects associated with adherence to oral hypoglycemic drugs, antihypertensive drugs, and statins among patients with diabetes. This study did not find a significant effect of adherence to these drugs on long-term mortality.
find an adherence-mortality gradient but was confined to 1 year of follow-up and did not try to disentangle any healthy adherer effect. The mortality benefits associated with high placebo adherence in randomized controlled trials raise questions about whether the adherence-mortality relationship is predominantly attributable to healthy adherer effects rather than to drug effects.4 Ours was the first study to our knowledge to demonstrate the existence of drug class-specific adherence-mortality gradients among real-world populations, a finding consistent with the biological responsiveness related to the pharmacological classes themselves.1,2,13 A meta-analysis of randomized clinical trials of secondary prevention found that statin use was associated with a 21% relative risk reduction in all-cause mortality.2 Our observations, which demonstrated modest superiority in favor of statins over β-blockers, may have also been attributable to interclass differences in biological responsiveness in long-term post-MI disease settings. Indeed, some have argued that the incremental survival benefits associated with β-blocker therapy in the thrombolytic era, especially among lower-risk AMI populations with preserved left ventricular function, may be modest at best and less pronounced than those observed for other evidence-based pharmacotherapies.25 Nonetheless, the relative mortality risk reductions associated with β-blocker adherence in our study were generally consistent in magnitude with those observed in randomized clinical trials comparing β-blockers to placebo.26,27

While less than 3.5% of our cohort had only nominal exposure to their corresponding drug of interest during the first year (as defined by a PDC <10%), the adherence rates observed in our study were similar to those reported elsewhere.28–30 For example, Andrade et al28 found among American Health Maintenance Organization enrollees that the discontinuation rate 1 year after initiation of statin treatment was 15%, which is similar to the 13% discontinuation rate observed in our study when examined over the entire follow-up period. Moreover, adherence propensity was not adversely affected by concomitant medications and, indeed, was higher among those already receiving evidence-based therapies prior to the index AMI.29

Our study was restricted to elderly populations, in part by design. In Canada, medication costs are covered by third-party payers. Accordingly, affordability factors and socioeconomic position should not have and did not
affect adherence. However, given their higher baseline cardiovascular risk and poorer tolerability to medications, se-

nors are among the most vulnerable subgroup in the population. Although clinical trials have rarely demon-

strated significant heterogeneity in treatment effects across age groups, one would reasonably assume that vari-

tions in baseline cardiovascular risk and compliance profiles across subpopula-

tions might alter the magnitude of as-

sociation between adherence and sur-

vival.

Our study has important clinical and policy implications. The graded dose-

response–type relationship underscres the importance of drug adher-

ence when projecting the survival benefits of evidence-based therapies in the population. Moreover, the long-

term prognostic importance associated with shorter-term adherence patterns (as measured within the first year of AMI dis-

charge) may have clinical applications for integration into cardiovascular prognostic indexes—indexes that might then be used to better delineate high-risk vul-

nerable populations who may benefit from more intensive secondary prevent-

tion initiatives.3 Finally, given their as-

sociated effects on survival, the inclu-

sion of adherence data will have important cost-effective implications and should be considered routinely in phar-

macoeconomic analyses.31

Our study has several noteworthy limitations. First, the therapies exam-

ined in our study were selected based on prespecified hypotheses and were not necessarily intended to represent the adherence-mortality patterns asso-

ciated with all secondary prevention pharmacotherapies. Moreover, our in-

ability to track medications pur-

chased over the counter (eg, aspirin) and the absence of other key clinical variables (eg, left ventricular func-

tion, symptom status) both limited our scope of therapies and the comprehen-

siveness of risk adjustment. Nonethe-

less, our analysis did adjust for many factors, including comorbidity, risk se-

verity, and concomitant and preexist-

ing use of evidence-based therapies.

Moreover, multiple sensitivity analy-

ses confirmed the robustness of our findings.

Second, our data contain no infor-

mation regarding potential adverse re-

actions, allergies, or intolerance, all of which might explain early discontinuation of therapy. Nonetheless, avail-

able evidence has shown that the inci-

dence of adverse drug reactions is relatively low, generally occurs dur-

ing the early rather than late phases of therapy, and is unlikely to entirely ac-

count for nonadherence, especially to statins or other preventive thera-

pies.32,33

Third, we used prescriptions to es-

imate adherence and had no informa-

tion on actual medication adherence or other healthy lifestyle behaviors (eg, smoking cessation, diet, and physical activity).34,35 Nonetheless, our mea-

sure of adherence is consistent with those used in other studies,36 has been shown to correlate with pill counts,37,38 and is not subject to recall bias.39 More-

over, adherence patterns to medica-

tions likely serve as reasonable surro-

gates for other adherent lifestyle behaviors.4

Finally, our study was confined to AMI patients in Ontario. Although the extent to which our findings are gen-

eralizable to other jurisdictions and dis-

dase settings is unknown, our study is comprehensive, consisting of all se-

nors in the largest province of Canada. Therefore, there is no reason to be-

lieve that our findings would not be generalizable to other jurisdictions that have similar drug reimbursement poli-

cies to that of Canada.

In conclusion, the differential class effects of drug adherence on long-term survival following MI suggest that adherence-related mortality benefits associated with evidence-based pharmacotherapies are mediated by drug effects more so than by generic healthy adherer behavioral attributes. The beneficial biological effects associ-

ated with higher drug adherence on survival underscores the need to opti-

mize adherent patient behavior pat-

terns to maximize the survival gains of evidence-based therapies in real-world populations, which may be enhanced through the implementation of phar-

macy or other preventive care pro-

grams.40

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Study concept and design: Rasmussen, Alter

Acquisition of data: Rasmussen, Chong, Alter

Analysis and interpretation of data: Rasmussen, Chong, Alter

Drafting of the manuscript: Rasmussen, Alter

Critical revision of the manuscript for important in-

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