Sex Disparities in Post-Acute Myocardial Infarction Pharmacologic Treatment Initiation and Adherence

Problem for Young Women

Kate Smolina, PhD; Laura Ball, MPH; Karin H. Humphries, MBA, DSc; Nadia Khan, MSc, MD; Steven G. Morgan, PhD

Background—The prevalence of the use of secondary prevention cardiovascular medications is lower among women than men, but it is unclear if this is a result of lower treatment initiation among women or lower treatment adherence. We aimed to map the treatment pathway for survivors of acute myocardial infarction (AMI) by sex and age.

Methods and Results—This retrospective population-based cohort study used linked administrative data sets in British Columbia (2004–2011), which include health care, prescription drugs, sociodemographic, and mortality information. The study cohort included all individuals admitted to hospital for AMI in 2007–2009 and survived for 1 year after hospital discharge. Patients were evaluated for whether they initiated and then subsequently filled prescriptions angiotensin-converting enzyme inhibitors, β-blockers, and statins. More than two thirds of AMI survivors initiated treatment on all appropriate medications, given their contraindications, within 2 months of discharge. Younger men were significantly more likely than younger women to initiate appropriate treatment (adjusted odds ratio, 1.38; 95% confidence interval, 1.10–1.75). By the end of 1 year after discharge, only one third of all AMI survivors filled all appropriate prescriptions for at least 80% of the year. There was no significant difference in adherence to medication therapy between women and men.

Conclusions—The majority of AMI survivors either discontinue treatment or do not refill their prescriptions consistently. Women <55 years are significantly less likely to be on optimal therapy by the end of 1 year after discharge, which is driven by a sex disparity in treatment initiation and not treatment adherence. (Circ Cardiovasc Qual Outcomes. 2015;8:586-592. DOI: 10.1161/CIRCOUTCOMES.115.001987.)

Key Words: cohort studies ■ myocardial infarction ■ odds ratio ■ prevalence ■ survivors

Methods

We aimed to map the treatment pathway for AMI survivors and to investigate sex differences in pharmaceutical treatment initiation after discharge and subsequent adherence to treatment during the following year by age group. The cascade of care is an approach commonly used by HIV/AIDS researchers to illustrate the number of people at each stage of treatment to identify implementation gaps in HIV care. We applied this concept to illustrate the trajectory of pharmaceutical treatment in AMI survivors. Stratification by sex and age allows us to identify points along the care trajectory where gaps in treatment differentially affect women.

Data Sources

Our analysis is based on deidentified linked health data sets provided by Population Data British Columbia (BC) for 2004 to 2011 with approval of relevant data stewards and the University of British Columbia’s Behavioural Research Ethics Board. This study was approved by the University of British Columbia’s Behavioural Research Ethics Board (H11-02273; October 24, 2011). Data sets included health care, sociodemographic, and mortality information for all British Columbians (population 4.5 million) except those whose prescription drug coverage fell under federal jurisdiction (military veterans, registered First Nations people and Inuit, and federal penitentiary
WHAT IS KNOWN
• Evidence-based cardiovascular medicines for secondary prevention can help to reduce the risk of recurrent events.
• Women are less likely to receive appropriate pharmacotherapy after an acute myocardial infarction.

WHAT THE STUDY ADDS
• This study examines whether lower medication use by women in an outpatient setting is a result of lower treatment initiation or lower treatment adherence.
• Younger women are significantly less likely to initiate treatment after infarct.

Smolina et al
Sex Disparities in Post-AMI Drug Treatment
587

inmates, which collectively make up ≈4% of the BC population). To ensure complete data capture for study subjects, we focused our analysis on individuals living in BC for at least 275 days in each year during the study period.

Our hospital services data came from the Discharge Abstract Database, which tracks separations from all hospitals in BC. Hospital records contain information about reason for admission, length of stay, level of care, procedures received, and ≤25 diagnoses coded using the International Classification of Diseases (ICD), version 10. Our medical services data included provider type, service type, cost of service, and 1 primary diagnosis code (ICD-9/10) for every fee-for-service medical visit by all patients in our data set.

Our data on prescription drug purchases came from BC PharmaNet, an information system into which pharmacists must enter records of every prescription dispensed outside of acute care hospitals, regardless of patient age or insurance status. Prescription records include information about the drug type, dose, quantity dispensed, formulation, and cost. We excluded nonprescription drugs as pharmacists are not required to enter their purchase into PharmaNet. Therefore, we were unable to identify the use of aspirin, one of medicines indicated for post-AMI secondary prevention. We used the World Health Organization’s Anatomic Therapeutic Chemical drug classification system to identify medications of interest (see Table I in the Data Supplement for specific Anatomic Therapeutic Chemical codes).14

Study Cohort Information
We identified all patients who were admitted to hospital between January 1, 2007 and December 31, 2009 with a primary diagnosis of AMI (ICD-10 codes I21 or I22).16 AMI events were classified either as ST–elevation myocardial infarction (ICD-10 codes I21.0-I21.3, I22.0, I22.1, I22.8) or non–ST-segment–elevation myocardial infarction (ICD-10 codes I21.4, I21.9, I22.9). We restricted our analysis to those who were aged 20 to 99 years, had a length of stay between 1 day and 3 months for AMI hospitalization, survived for 1 year after discharge, and did not reside in a long-term care facility. To identify incident AMI cases, those who had a previous AMI were excluded. We enforced a 1-year survival restriction to have a consistent patient cohort to measure both initiation and adherence and to illustrate the cascade of care. This requirement lead to an exclusion of 1019 individuals, or 7.5%, of all those hospitalized for AMI.

Pharmacotherapy Treatment, Adherence, and Optimal Therapy
Medications of interest in this analysis were β-receptor antagonists (β-blockers or BBs), cholesterol-lowering statins, and either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. We constructed variables indicating the use of each medication of interest before the index AMI event and initiation after the event. Pre-AMI medication use was defined as having ≥1 prescription dispensed within 6 months after the index event. Post-AMI initiation of each drug was said to have occurred if a patient filled a prescription within 60 days after hospital discharge. If individuals had previous use, post-AMI initiation of each of drug was said to have occurred if they filled a prescription within 60 days of discharge or within 60 days after the previous prescription ran out, whichever came first.

Appropriate therapy was defined as filling prescriptions for all evidence-based drugs, given patients’ contraindications. We flagged if a patient had a relative or absolute contraindication to any of the 3 drug classes under study. We defined contraindications for the drugs as follows: (1) pregnancy at index hospitalization (all drugs), (2) asthma and nondrug-induced bradycardia (BBs), (3) cirrhosis (statins), and (4) renal failure and hyperkalemia (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; see Table II in the Data Supplement for ICD-9 and ICD-10 codes).17 Contraindications were identified using ICD-9 and ICD-10 diagnostic codes recorded at the index admission and during other hospital admissions and physician visits ≤1 year before index AMI.

Adherence was assessed using the proportion of days covered, which is calculated as the total number of days supplied for all prescriptions filled, divided by 365 days, after discharge from index AMI. For prescriptions that had an end date after the 1 year mark, only days that fell during the period of interest were counted. By definition, proportion of days covered was only calculated for those who had filled at least 1 prescription. For each drug class, a proportion of days covered value of ≥0.8 was defined as adherent and <0.8 was defined as nonadherent. This definition of adherence is consistent with previous studies.18,19

Optimal pharmacotherapy was a composite measure of filling enough prescriptions for all appropriate medications to have proportion of days covered ≥0.8 for all medications during 1 year after discharge.

Potential Confounding Variables
Registration data sets for the universal public health insurance plan provided basic demographic information concerning age, sex, and area of residence for all individuals in our cohort. To this, we added additional information concerning patient ethnicity and income. The dominant ethnic minorities in BC are Chinese and South Asian, respectively comprising 40% and 26% of the provinces’ visible minority population as of the 2006 census.20 Because there are no population-based sources of information on ethnicity that could be linked to BC’s health research data sets, we ascertained ethnicity using an algorithm developed to identify surnames of South Asian and Chinese origin and validated for use with data from secondary sources.21

We estimated household income based on a combination of household-specific and area-based income data.22 For 81% of the population, we had validated, household-specific income information from the registration files for BC’s universal, income-based public drug subsidy system (Fair PharmaCare). For the remaining 19% of the population, we estimated household income based on the median household income for the Census Dissemination Area (population 400–700), in which people lived. An income quintile was assigned to each individual in the study cohort in reference to the BC population.

We used the John Hopkins Adjusted Clinical Group (version 10.0) case-mix adjustment system with ICD codes drawn from each individual’s medical and hospital records.17 We used selections from the 264 Expanded Diagnostic Clusters of the Adjusted Clinical Group system to flag comorbidities relevant to this study. Expanded Diagnostic Clusters group similar diagnosis codes for related conditions and were used to capture the diagnosis of relevant comorbidities (see Table III in the Data Supplement for specific codes).

Statistical Analysis
We used t tests and χ2 tests to compare baseline characteristics between women and men for continuous and categorical variables, respectively. We used logistic regression analysis to examine the sex
disparities in (1) initiation of appropriate pharmacotherapy, (2) adherence, and (3) receipt of optimal pharmacotherapy for each age group. We found significant age–sex interaction (P=0.032) and, therefore, we stratified the results of our models by age group. All analyses were conducted using SAS version 9.3 and STATA version 13.1.

**Results**

Of the 13,524 patients admitted to hospital for AMI between 2007 and 2009 in BC, 12,261 (90.7%) survived for at least a year after discharge. Table shows the characteristics of the study cohort. On average, women were almost 7 years older than men. Men were more likely to have ST–elevation myocardial infarction AMI when compared with women. Over half of women in our cohort were in the lowest income quintile, compared with less than a third among men. Ethnic distribution of the study cohort was generally consistent with provincial statistics.

Approximately half of the study cohort had at least 1 prescription for a study drug before their index AMI event. Majority of men and women had no contraindications to evidence-based medications. Only 4.0% of women and 3.4% of men did not initiate any pharmaceutical treatment within 2 months of discharge from hospital.

The cascade of care, shown in Figure 1, depicts the trajectory of pharmacotherapy for AMI survivors by age. The greatest sex disparity is observed for initiation of all appropriate medications within 2 months after discharge. The figure also indicates that women and men do not appreciably differ in adherence, once treatment has been initiated: a similar proportion of those who initiated therapy did not continue with it between 6 and 12 months after discharge. By the end of 1 year after being discharged from index AMI hospitalization, just over a third of survivors are on optimal therapy, that is, filling prescriptions for all appropriate medications for at least 80% of the year.

Figure 2 illustrates that initiation of appropriate therapy was lower among women. It also shows that women are less likely to initiate appropriate pharmaceutical treatment across all ages. However, the greatest disparity occurs in the 20 to 54 year age group (75% of men compared with 65% of women). Notably, initiation of appropriate therapies was lowest in the 85+ age group for both the sexes (50% of men and 48% of women). Analysis by drug class indicated that women have a higher likelihood of undertreatment for each drug class (range, 82%–84%) compared with men (range, 85%–90%), but undertreatment was most pronounced when all the 3 drug types were considered together (64% for women versus 72% for men).

Adherence to medications for which prescriptions were filled during 1 year after discharge was similar between men and women and across age groups, ranging between 42% and 50%. Although there were no statistically significant differences by drug class, women were slightly more likely to be adherent to BBs and angiotensin-converting enzyme/angiotensin receptor blockers, whereas men were slightly more likely to be adherent to statins.

**Analyses**

Figure 3 shows the results of regressions comparing men with women in each age group. Men are more likely to initiate appropriate treatment (ie, fill prescriptions for all appropriate drugs within 2 months of discharge after AMI) in all age groups, after adjusting for income, ethnicity, comorbidities, in-hospital procedures, and previous medication use. This
relationship is most pronounced in those <65 years (adjusted odds ratio, 1.38; 95% confidence interval, 1.10–1.75 for 20–54 year olds and adjusted odds ratio, 1.38; 95% confidence interval, 1.13–1.68 for 55–64 year olds).

Sex differences in adherence to treatment were not statistically significant for any age group. We repeated adherence analysis by drug class and there were no significant sex differences in any age group either.

There were no sex differences in being on optimal therapy, with the exception of men in the youngest age group who were more likely to be optimal therapy during the first year after discharge (adjusted odds ratio, 1.30; 95% confidence interval, 1.03–1.63).

**Discussion**

We report significant sex disparities in initiation of appropriate pharmacotherapy after AMI, particularly in younger women. However, we found no appreciable differences between men and women in treatment adherence. Alarmingly, only a small proportion of patients are receiving optimal therapy during 1-year post-AMI.

The drivers behind sex disparity in treatment are not well understood. It is thought to be a result of several factors, including differences in symptom presentation, perceived risk of secondary events, concerns about limited information about the safety and effectiveness of these drugs in women, physician biases, and demographic factors, such as differences in age and socioeconomic status. There is a need for qualitative research on the reasons for underuse of evidence-based treatment among younger women.

In this study, we show that the sex disparity in pharmacotherapy initiation may not be universal but rather limited to younger age groups. Cardiovascular disease among younger women has only recently received research attention, or it is possible that the perception of risk for adverse outcomes—by physicians and patients—is still skewed for younger women, who are seen as healthy and at low risk. Our findings suggest that clinicians and patients may benefit from better education and awareness of undertreatment of younger women.

**Figure 1.** Cascade of care among 1-year survivors of acute myocardial infarction (AMI); (A) age 20 to 64 years and (B) age 65+ years.

**Figure 2.** Initiation on appropriate therapy within 2 months of discharge, by sex and age group.
who experience an AMI. Possible standardization of discharge prescriptions could be explored.

### Adherence to Pharmacotherapy

Post-AMI medications are intended to be taken on a daily basis indefinitely. Nonadherence is a significant problem in AMI survivors, potentially contributing to poor health outcomes and excess mortality. We found that the overall levels of adherence were suboptimal for the majority of our study cohort. The World Health Organization recognizes adherence to long-term therapy as a multidimensional phenomenon that is influenced by several factors, including socioeconomic circumstances, the structure and function of the healthcare system, disease-related factors, therapy-related factors, and patient-related factors. Healthcare professionals could benefit from training in adherence management that focuses on assessment and mitigation of all factors that influence adherence. Patients with AMI (both men and women) may need ongoing—and likely multiple—interventions, including support, education, and encouragement to improve long-term compliance with prescribed treatment.

We found no significant differences in overall adherence to all prescribed medications between men and women or between drug classes. Comparison with other studies is not straightforward; the literature on sex-based disparities in adherence to cardiovascular drugs is mixed and results vary by drug class; some studies show that women have better adherence to angiotensin-converting enzyme inhibitor/angiotensin receptor blockers and BBs or statins, whereas others reveal that men have better adherence to statins, BBs, and aspirin. This between-study variation may be partially attributable to the structure of the healthcare system and drug reimbursement, differences in prescribing practices across jurisdictions, and differences in adherence measurement. A recent meta-analysis on sex and racial disparities in adherence to statin therapy reported higher nonadherence to statins among women <65 years (odds ratio, 1.11; 95% confidence interval, 1.08–1.07). We also observed lower adherence in women than men among those aged 20 to 54 years. The reasons for the lower adherence among younger women in our study are unclear. Similar to treatment initiation, this may be a result of the traditional thinking that cardiovascular disease is a man’s disease, influencing female patients’ perceptions of their risk of a recurrent event or death, especially at a young age.

### Optimal Pharmacotherapy

The proportion of patients receiving optimal pharmacotherapy by the end of the first year post-AMI discharge for all classes was low: only 1 in 3 women and men filled enough prescriptions for evidence-based treatment to cover at least 80% of the time. The sex disparity was significant only among the youngest age group, mostly driven by lower treatment initiation in women. Among those aged 55 to 64 years, the under initiation among women was offset by lower adherence among men, with no significant difference in the overall receipt of optimal therapy. Newby et al found that only 21% of patients with coronary artery disease in the United States consistently used aspirin, BB, and lipid-lowering therapy between 1995 and 2002. This is a lower proportion than we found, however, the Newby study did not adjust for contraindications so a greater proportion may have been on optimal pharmacotherapy as defined in our study.

In sum, our findings demonstrate that lower rates of the use of secondary prevention medications among women are concentrated in the younger age groups and driven by disparities in treatment initiation and not treatment adherence. Therefore, the first few months after hospital discharge are critical in clinical management of younger patients with AMI to prevent recurrent events.

### Strengths and Limitations

A key advantage of this study is that the data are population-based and include all BC residents, reflecting standard clinical practice in the province. Our data are comprehensive and capture all dispensed prescriptions, and not restricted to certain care facilities, age groups, or subpopulations. Our study also adds to the literature as many previous studies have not adjusted for contraindications in their investigation of post-AMI sex disparities in pharmaceutical use. Furthermore, several
studies on this topic only analyzed medications prescribed at discharge,\textsuperscript{11,40,41} whereas our data allow us to capture prescriptions filled after hospital discharge, thereby giving us a more accurate measure of initiation.

We were unable to determine whether sex-based differences in treatment initiation were driven by physician prescribing practices or patient behavior because PharmaNet database only captures filled prescriptions. Our measure of adherence is indirect and overestimates adherence in those individuals who fill prescriptions but do not take them. It is possible that we may have misclassified patients as being eligible for particular treatment—the contraindications to therapy that we included in our analysis were absolute contraindications and were meant to capture the majority of cases where the use of the drug class should not occur. However, the use of therapy in individuals with relative contraindications requires clinical judgment. As a result, a small number of patients may have been classified as undertreated when there was a clinically valid reason for not receiving treatment. However, we would not expect that missed contraindications or intolerance would differentially affect women or men, thus these limitations are unlikely to meaningfully affect our findings. Our inability to examine the use of aspirin and thus the full complement of recommended post-AMI medications, possibly led to an overestimate of the proportion of patients who were receiving truly optimal therapy. We were also unable to ascertain blood pressure values and lipid levels. Our results only apply to 1-year survivors of AMI, given our selection criteria. However, that represents the vast majority (92.5\%) of all individuals admitted to hospital for AMI.

Conclusions

We found that women <55 years are significantly less likely to be on optimal therapy by the end of 1 year after discharge, which is driven by a sex disparity in treatment initiation and not treatment adherence. For other age groups, slight under initiation on therapy among women seems to be offset by lower adherence to treatment among men. Overall, the majority of AMI survivors either discontinue treatment or do not refill their prescriptions consistently, suggesting that further improvements in post-AMI treatment management are necessary.

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Disclosures

None.

References


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### Table 1. ATC code classification for drugs of interest

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drugs Included</th>
<th>ATC level 5 Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-blockers</td>
<td>exprenolol, pindolol, timolol, nadolol, metoprolol, atenolol, acebutolol, bisoprolol, labetalol, carvedilol</td>
<td>C07AA02, C07AA03, C07AA06 (oral), C07AA12-C07AG02</td>
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<tr>
<td>Statins</td>
<td>simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, lovastatin and nicotinic acid</td>
<td>C10AA01-05, C10AA07, C10BA01</td>
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<tr>
<td>ACEI</td>
<td>captopril, enalapril, lisinopril, perindopril, ramipril, quinapril, benazepril, cilazapril, fosinopril, trandolapril, enalapril and diuretics, lisinopril and diuretics, perindopril and diuretics, ramipril and diuretics, quinapril and diuretics, cilazapril and diuretics, trandolapril and verapamil</td>
<td>C09AA01-C09BB10</td>
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<tr>
<td>ARB</td>
<td>losartan, eprosartan, valsartan, irbesartan, candesartan, telmisartan, olmesartan medoxomil, losartan and diuretics, eprosartan and diuretics, valsartan and diuretics, irbesartan and diuretics, candersartan and diuretics, telmisartan and diuretics, olmesartan medoxomil and diuretics, telmisartan and amlodipine</td>
<td>C09CA01-C09DB04</td>
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Table 2: ICD-9 and ICD-10 codes for contraindications

<table>
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<tr>
<th>Contraindication</th>
<th>ICD 10 Codes</th>
<th>ICD 9 Codes</th>
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<tr>
<td>Asthma</td>
<td>J45.909</td>
<td>493.x,</td>
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<td>Bradycardia</td>
<td>R00.1x</td>
<td>427.89</td>
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<tr>
<td>Chronic renal failure</td>
<td>I12xx, I13xx, N18.xx, T82.4x, Z99.2x</td>
<td>585.x, 403.x, 404.x, 996.7, V451</td>
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<tr>
<td>Hyperkalemia</td>
<td>E87.5x</td>
<td>276.7, 276.8</td>
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<tr>
<td>Liver disease (cirrhosis)</td>
<td>K70xx, K73xx, K74xx</td>
<td>571</td>
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<tr>
<td>Pregnancy*</td>
<td>O00xx, O01xx, O02xx, O03xx, O04xx, O05xx, O06xx, O07xx O08xx, O9Axx or if gestational age not missing</td>
<td>V22.0-V22.2 or if gestational age not missing</td>
</tr>
<tr>
<td>Renal failure</td>
<td>N17.xx, N19xx, R34xx</td>
<td>584.x, 586.x, 788.5</td>
</tr>
</tbody>
</table>

*During index hospitalization only

Table 3: EDC codes for comorbidities

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>EDC code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmia</td>
<td>CAR09</td>
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<tr>
<td>Cancer</td>
<td>MAL04 – MAL15, MAL18</td>
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<tr>
<td>Cerebrovascular disease</td>
<td>NUR05</td>
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<tr>
<td>Depression</td>
<td>PSY09</td>
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<tr>
<td>Diabetes</td>
<td>END06 – END09</td>
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<tr>
<td>Heart failure</td>
<td>CAR05</td>
</tr>
<tr>
<td>Hypertension</td>
<td>CAR14, CAR15</td>
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<tr>
<td>Ischaemic heart disease</td>
<td>CAR03</td>
</tr>
<tr>
<td>Liver disease</td>
<td>GAS05</td>
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<tr>
<td>Peripheral vascular disease</td>
<td>GSU11</td>
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<tr>
<td>Renal disease</td>
<td>REN01, REN05</td>
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<tr>
<td>Respiratory disease</td>
<td>RES10, RES11</td>
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