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Am J Med. Author manuscript; available in PMC 2013 September 12.

Published in final edited form as:
Am J Med. 2009 October ; 122(10): 961.e7–961.13. doi:10.1016/j.amjmed.2008.12.021.

Long-term Medication Adherence after Myocardial Infarction: experience of a community

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Abstract

Background—Adherence to evidence-based medications after myocardial infarction is associated with improved outcomes. However, long-term data on factors affecting medication adherence after myocardial infarction are lacking.

Methods—Olmsted County residents hospitalized with myocardial infarction from 1997-2006 were identified. Adherence to HMG-CoA reductase inhibitors (statins), beta blockers, angiotensin-converting enzyme inhibitors (ACE Inhibitors), and angiotensin II receptor blockers (ARB), were examined. Cox proportional hazard regression was used to determine the factors associated with medication adherence over time.

Results—Among 292 persons with incident myocardial infarction (63% men, mean age 65 years), patients were followed for an average of 52±31 months. Adherence to guideline-recommended medications declined over time, with 3-year medication continuation rates of 44%, 48%, and 43% for statins, beta blockers, and ACE Inhibitors/ARB, respectively. Enrollment in a cardiac rehabilitation program was associated with an improved likelihood of continuing medications, with adjusted hazard ratio (95% confidence interval) for discontinuation of statins and beta blockers among cardiac rehabilitation participants of 0.66 (0.45-0.92) and 0.70 (0.49-0.98), respectively. Smoking at the time of myocardial infarction was associated with a decreased likelihood of continuing medications, though results did not reach statistical

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Disclosures:
The authors state the there are no potential conflicts of interest to disclose.

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significance. There were no observed associations between demographic characteristics, clinical characteristics of the myocardial infarction and medication adherence.

Conclusions—After myocardial infarction, a large proportion of patients discontinue use of medications over time. Enrollment in cardiac rehabilitation after myocardial infarction is associated with improved medication adherence.

Keywords

Myocardial infarction; drugs; adherence; cardiac rehabilitation

INTRODUCTION

There has been an increasing interest in recent years to improve the uptake of evidence based treatment after myocardial infarction.[1-3] A number of studies have shown that discharge prescriptions for aspirin, beta-blockers, angiotensin converting enzyme inhibitors, and cholesterol lowering therapy after a myocardial infarction are associated with improved outcomes.[4-6] Adherence to these evidence-based medications for secondary prevention is associated with further improvement in outcomes.[7, 8] Thus, there is an increasing interest in understanding the prescription patterns and discontinuation of these medications among patients with acute myocardial infarction.

Prior studies have demonstrated that adherence to medications after hospital discharge for myocardial infarction is poor.[9-12] For instance, a study among myocardial infarction patients in Ontario, Canada noted that 26% of patients failed to fill all of their prescriptions within 120 days of hospital discharge, and these patients experienced increased mortality compared with those who filled all prescriptions.[9] In addition, studies have suggested that many patients discontinue use of cardioprotective medications over time, with 13%, 12%, and 20% of patients discontinuing use of statins, beta blockers, and angiotensin converting enzyme inhibitors, respectively, 6 months after discharge in a separate study.[11] However, the length of follow-up after myocardial infarction is very limited in most studies, such that little is known about medication adherence more than one year post- myocardial infarction. Further, many of the studies have been conducted using claims data with limited clinical information about the population. Thus, there is limited research on factors associated with long-term adherence for evidence-based medication use after a myocardial infarction.

The present study is aimed at addressing these gaps in knowledge by using a cohort of patients for whom longitudinal data, as well as clinical characteristics, are available. The goals of this study were first, to determine long-term adherence to guideline-recommended therapies and second, to determine the factors associated with long-term medication adherence among these patients.

METHODS

Study Population

Olmsted County is located in southeastern Minnesota with a population of 124,277 according to the 2005 Census (90% Caucasian, 51% female). Nearly all medical care is provided by relatively few providers, including the Mayo Clinic, Olmsted Medical Center, and a few private practitioners. Each provider in the community uses a single medical record for each patient. Through the Rochester Epidemiology Project, this information is extensively indexed, resulting in the linkage of all medical records from all sources of care through a centralized system.[13] The population for this study consisted of a subset for whom pharmacy claims data were available (Figure 1).

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Case Definition and Enrollment

All Olmsted County residents hospitalized from 1997-2006 with a troponin T level ≥0.03 ng/mL (Troponin T Stat Assay, Roche Diagnostics, Indianapolis, IN) were prospectively identified within twelve hours of the blood draw and approached for consent and enrollment in the parent study. Myocardial infarction was defined according to published recommendations,[14] which define myocardial infarction based on cardiac pain, electrocardiographic data (using Minnesota coding),[15] and biomarker levels. The reliability of this data has been validated.[16, 17] Those patients with confirmed myocardial infarction for whom prescription claims data were available (via an employer-sponsored health plan claims database) were included in the present study. Under this plan, enrollees had generous prescription drug coverage with monthly copayments of $5 for generic drugs and $10 for branded drugs (after 2004 enrollees were able to get a 3-month supply of generic drugs for $5 through mail order).

Additional Patient Data

Baseline patient characteristics were collected from the medical record by nurse abstractors. Measurements recorded at the closest time to the index myocardial infarction were used. Smoking was categorized as current or past. Diabetes, hypertension, and hyperlipidemia were defined by physician diagnosis. The number of comorbidities were determined from those comorbidities used to calculate the Charlson comorbidity index.[18] Family history of coronary disease was ascertained from the medical record. Reperfusion was defined as thrombolysis or coronary angioplasty within 24 hours after admission. ST-segment elevation was defined by the Minnesota code. Medications prescribed at the time of hospital discharge were abstracted from the hospital dismissal summary. Data on enrollment in cardiac rehabilitation were obtained from the healthcare claims database and the medical record. Enrollment in a cardiac rehabilitation program was defined as attending at least one cardiac rehabilitation program session within 1-month after myocardial infarction. Referral to cardiac rehabilitation is a standard part of the institutional practice for myocardial infarction patients.

Outcomes

Three classes of prescription medications were evaluated based on evidence-based guidelines for care after myocardial infarction: ACE Inhibitors or angiotensin II receptor blockers (ARB), beta-blockers, and HMG-CoA reductase inhibitors (statins). Aspirin use could not be assessed due to a lack of data on non-prescription drug use in this cohort. Not every patient with myocardial infarction was prescribed a medication from each medication class at the time of hospital discharge. The recommended medications for each patient at the time of hospital discharge were abstracted from the hospital dismissal summary medication list. Subsequently, prescription claims data from a self-funded health plan were obtained through a prescription claims database which contains information on medication prescriptions filled and the start and end dates of every prescription. Each patient's medication adherence to filled prescriptions was constructed using data from the prescription claims database. A continuous exposure period was defined by the period of time prescriptions were refilled at intervals no greater than 90 days after the end of the previous prescription for each of the three classes of medications. A change in medication within the same class was considered continuation of therapy, provided it was done within the 90-day refill interval. Refill intervals used to define continuous exposure of 60- and 120-days were evaluated and did not affect the results.

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Statistical Analysis

Baseline characteristics are presented as frequencies or means with standard deviations. We evaluated the factors associated with filling at least one prescription for each of the medication classes using logistic regression. Potential factors included age, sex, smoking status, in hospital revascularization/ reperfusion therapy, ST elevation myocardial infarction, family history of coronary disease and the number of comorbidities identified at the time of myocardial infarction. Subsequently, for each medication class (statin, beta blocker, ACE Inhibitors and/or ARB) only patients filling at least one prescription were included in medication adherence analysis for that particular medication class. Medication adherence over time was assessed using the Kaplan-Meier method with censoring at the end of the observation period or at the time of death. Cox proportional hazard regression analysis was utilized to examine potential factors associated with duration of medication adherence for each of the three medication classes. Potential factors for medication adherence were included in the models using forced entry and included age, sex, smoking status, in hospital revascularization/ reperfusion therapy, enrollment in a cardiac rehabilitation program, and the number of comorbidities identified at the time of myocardial infarction. All statistical analyses were performed using the statistical software Stata version 10.0.

RESULTS

Baseline characteristics

A total of 1692 Olmsted County residents with incident myocardial infarction were identified from 1997-2006. Of these, 292 were members of a specific employer-sponsored health plan with prescription drug data available, and were included in the present analysis (Figure 1). The mean age of participants was 65±15 years, 184 (63%) were male, and 191 (65%) enrolled in cardiac rehabilitation after their index myocardial infarction (Table 1).

Medication adherence in the community

Following hospital discharge, 75%, 84%, and 62% of patients filled a prescription for statins, beta blockers, and ACE Inhibitors/ARB, respectively. Additionally, based on discharge records very few subjects prescribed these medications did not get their prescriptions filled (3 for statins, 5 for beta-blockers, and 6 for ACE-inhibitors). This is not surprising because all the subjects in this study were well insured. In multivariable analyses including age, sex, smoking status, in hospital revascularization/ reperfusion therapy, ST elevation myocardial infarction, family history of coronary disease and the number of comorbidities identified at the time of myocardial infarction, we did not observe any significant demographic or clinical factors associated with filling the medication prescriptions at discharge. Men trended towards a higher likelihood of filling prescription for statins (OR=1.77, 95% CI=0.99-3.17). Only patients filling a prescription in each unique medication class were included in subsequent medication adherence analyses (Figure 1). Mean follow-up for this entire sample was 52±31 months. Medication adherence decreased progressively over time, but was similar for beta-blockers, statins, and ACE Inhibitors/ARB (Figure 2). Among patients who filled a prescription for statins, 78%, 59%, and 44%, continued taking the medication at 12-, 24-, and 36-months, respectively. Similarly, continuation rates for beta-blockers were 79%, 63%, and 48%, and continuation rates for ACE Inhibitors/ARB were 73%, 55%, and 43% at 12-, 24-, and 36-months, respectively.

Factors Associated with Medication Adherence

Among variables assessed for their association with medication adherence, enrollment in a cardiac rehabilitation program was associated with a significant increase in the likelihood of continuing cardioprotective medications after myocardial infarction (Table 2). For instance,

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participation in a cardiac rehabilitation program was associated with a 34% decreased likelihood of discontinuing statin therapy over time compared with those who did not participate (adjusted hazard ratio 0.66, 95% confidence interval 0.45-0.92). A similar protective effect of enrollment in a cardiac rehabilitation program was observed for both beta blockers and ACE Inhibitors/ARB. The association between cardiac rehabilitation enrollment and medication adherence did not change according to the number of cardiac rehabilitation visits attended.

Among other factors explored, smoking at the time of myocardial infarction appeared to be associated with an increased likelihood of discontinuing cardioprotective medications, though the results were not statistically significant. No association between age, sex, in-hospital revascularization/ reperfusion therapy, or number of comorbidities and medication adherence were observed (Table 2). In ancillary analyses, we found no association between the number of medications filled per patient or the year of myocardial infarction and medication adherence.

As cardiac rehabilitation was the sole independent predictor of improved medication adherence in this study, in an ancillary analysis we examined the adherence to each medication class among cardiac rehabilitation participants vs. nonparticipants. Adherence to statins (p=0.002), beta blockers (p=0.012), and ACE Inhibitors/ARB (p=0.002) was better in those enrolling in a cardiac rehabilitation program (Figure 3). For example, at one year post-myocardial infarction, 80% of patients enrolled in cardiac rehabilitation remained on statin therapy vs. 61% who did not attend cardiac rehabilitation. Similarly, for beta blockers and ACE Inhibitors/ARB, 1-year medication continuation rates were 78% and 74% among those who attended cardiac rehabilitation vs. 62% and 54% among those who did not attend cardiac rehabilitation, respectively.

DISCUSSION

The present study demonstrates that a large proportion of patients discontinue use of prescribed cardioprotective medications after myocardial infarction, with less than 50% continuing medications at three years post- myocardial infarction. These results are particularly striking as they include a population enrolled in an employer-sponsored health plan with generous prescription drug coverage.

However, participation in cardiac rehabilitation after myocardial infarction was associated with improved adherence to cardioprotective medications compared with those who did not participate. Cardiac rehabilitation participation was an independent predictor of improved adherence to statin and beta blocker therapies after myocardial infarction, with similar trends observed for ACE Inhibitors/ARB.

Medication Adherence Following Myocardial Infarction

Secondary prevention focuses on risk reduction in patients with established coronary disease who are at high risk for future events and adverse outcomes. Patient adherence to guideline-recommended therapies after myocardial infarction has been associated with improvement in outcomes.[12, 19] Few studies have reported on medication adherence after myocardial infarction,[9, 11, 12, 20] with available studies demonstrating poor adherence among a large proportion of patients. Eagle et al reported on patients with unstable angina or myocardial infarction in the Global Registry of Acute Coronary Events (GRACE) study and noted that by 6 months post- myocardial infarction, 13%, 12%, and 20% of patients had discontinued their statin, beta blocker, and ACE Inhibitors, respectively.[11] Similarly, among 1521 patients enrolled in the PREMIER registry, results revealed that patients frequently discontinued evidence-based medications after myocardial infarction, with 12.1%

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discontinuing all cardioprotective medications by one month after myocardial infarction.[12] While these studies contribute important information regarding medication adherence after myocardial infarction, they frequently relied on self-reported medication use,[11, 12, 20] which is subject to recall bias, and may result in an overestimation of patient adherence.[21, 22] In addition, medication adherence was restricted to a follow-up period of less than one year in all cases, though lifelong use of evidence based medications are recommended after myocardial infarction.

The present study extends previous reports by examining medication adherence after myocardial infarction in a stable community population, using complete pharmacy records to determine medication adherence, and follows patients for an average of more than four years after myocardial infarction. Our findings indicate that a large proportion of patients discontinue use of cardioprotective medications over time, with less than 50% continuing statins, beta blockers, and ACE Inhibitors/ARB three years post- myocardial infarction. While previous reports have suggested that the time period immediately after myocardial infarction is a critical period for discontinuation of cardioprotective medications,[9, 12] our results indicated a steady rate of discontinuation throughout the follow-up period of the study.

Predictors of Medication Adherence Following Myocardial Infarction

Previous reports have demonstrated that patient use of guideline-recommended medications after myocardial infarction has been associated with patient clinical characteristics (age, education, income, number of medications before myocardial infarction),[9, 12] in-hospital care (attending cardiologist, discharge medication counseling) ,[9, 11] and early physician follow-up.[20] The present study extends previous reports by exploring the potential role of critical factors including cardiac rehabilitation participation in medication adherence after myocardial infarction.

The American Heart Association and the American College of Cardiology recommend the use of cardiac rehabilitation as a class I indication for secondary prevention after myocardial infarction, as well as for other cardiovascular disease conditions including coronary artery bypass grafting surgery, chronic stable angina and heart failure.[23-28] The goals for cardiac rehabilitation programs include medical evaluation, exercise training, cardiovascular disease risk factor modification with lifestyle and medical therapies, education, and counseling, with the aim to increase patient activity and physical functioning after a cardiac event, address psychosocial effects common after myocardial infarction, control cardiac symptoms, and manage coronary artery disease risk factors in an effort to stall or reverse the atherosclerotic process.[29, 30] Further, participation in cardiac rehabilitation after myocardial infarction has consistently been associated with decreased mortality.[31-33] Though several mechanisms have been proposed to explain how cardiac rehabilitation improves outcomes, including through improvement in lipid profiles,[34] decreased insulin resistance,[35] and improved psychological well-being,[36] the role of medication adherence has not been examined.

The findings of the present study suggest that, among factors explored, participation in cardiac rehabilitation after myocardial infarction is strongly and independently associated with improved adherence to both beta blockers and statins, medications that have been associated with improved outcomes after myocardial infarction.[37-39] Previous studies have documented that cardiac rehabilitation participation is associated with decreased mortality.[31, 40, 41] The findings observed herein suggest that improved adherence to evidence-based medications after myocardial infarction may represent a potential benefit of enrollment in cardiac rehabilitation. Certainly, the additional support and medical care that are given to cardiac rehabilitation program participants could logically contribute to

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continued use of cardioprotective medications. Furthermore, improved medication adherence could contribute to the mortality benefit consistently observed among cardiac rehabilitation participants, including our own cohort.[40] Alternatively, the observed association between medication adherence and cardiac rehabilitation participation may be attributable to a “healthy adherer” effect such that patients who are more likely to be adherent are also more likely to enroll in cardiac rehabilitation, rather than rehabilitation participation directly influencing medication adherence. More qualitative research may be necessary to better understand this association.

In the present study, we noted no association between medication adherence and either age or sex. Our findings are consistent with prior studies demonstrating no sex-based difference in medication adherence following myocardial infarction.[9, 11, 12] However, the association between age and medication adherence has been controversial, with some,[9, 12] but not all[11] studies demonstrating improved medication adherence in younger patients following myocardial infarction. Similarly, data on the association between smoking status and medication adherence after myocardial infarction is limited. A single study noted that there was no significant difference in continuation of cardioprotective medications after myocardial infarction according to smoking status.[12] In the present study, though smoking status was not a significant independent predictor of medication adherence following myocardial infarction, a trend toward worse adherence among current smokers was observed.

Strengths and Limitations

Potential limitations of the present study should be acknowledged to aid in data interpretation. First, data on medication adherence was only available for patients with administrative claims data available. Second, we do not have information regarding whether study patients discontinued medications due to documented intolerance or at the request of a physician. Finally, as with all cohort studies, differences observed could be a result of unmeasured confounding. Additionally, we were limited in the sample size in this study thus, the confidence intervals were wide in each of the multivariable analyses. The present study has several notable strengths. The cohort was community-based with a prolonged follow-up period and complete pharmacy records were used to determine medication adherence. In addition, as the entire cohort has health insurance, access to care, which is an important potential confounder in analyses of secondary prevention measures after myocardial infarction, cannot confound the present findings.

Conclusions

Among this community cohort of individuals, all part of an employer-sponsored health plan, cardioprotective medications are frequently discontinued after myocardial infarction. Enrollment in cardiac rehabilitation was associated with improved adherence to evidence-based medications.

Improved medication adherence may represent a novel benefit associated with cardiac rehabilitation and may contribute to observed improvement in outcomes among cardiac rehabilitation participants.

Acknowledgments

We would like to thank Susan Weston for providing detailed comments on the manuscript. We would also like to thank Sara Hobbs-Kohrt for assistance with manuscript preparation.

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NDS had access to data throughout the study and takes responsibility for the analysis. All other authors played important roles in conceptualization, data interpretation, writing, and critical revisions for this manuscript.

Funding Source: Mayo Foundation for Education and Research

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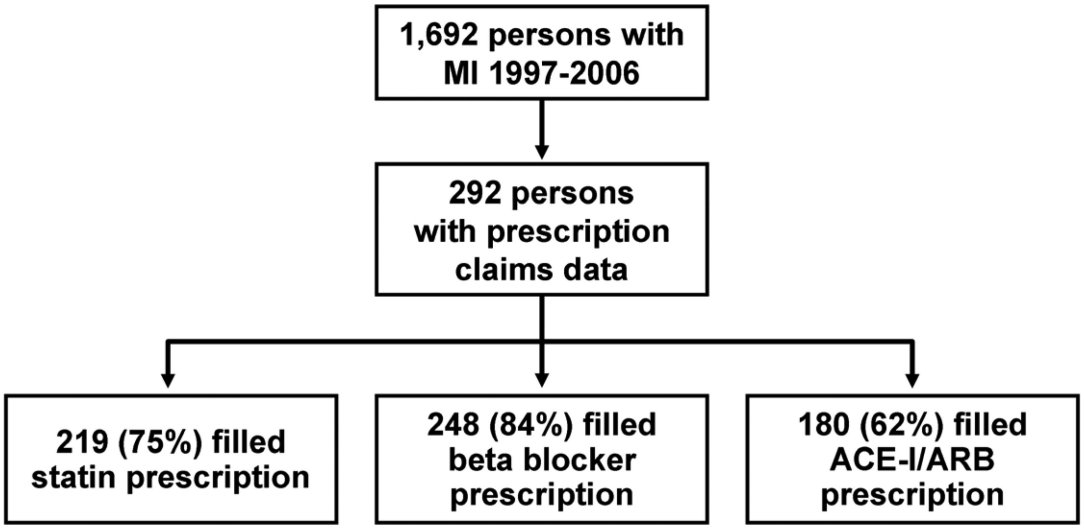

Figure 1. Study Population

MI= Myocardial infarction; ACE-I/ARB= angiotensin converting enzyme inhibitor/ angiotensin II receptor blocker

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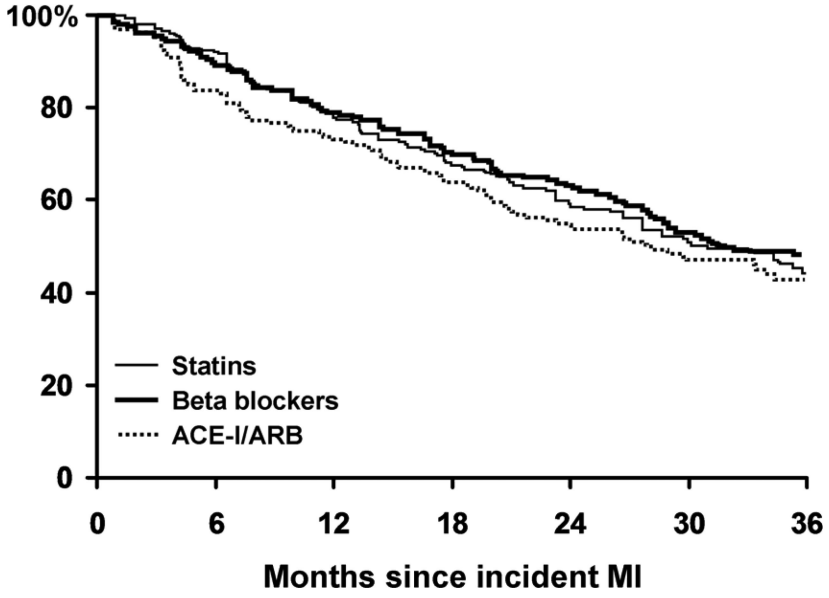

Figure 2. Medication Continuation After Myocardial Infarction in the Community

Caption: Percentage of patients continuing medications over time are shown. MI= Myocardial infarction; ACE-I/ARB= angiotensin converting enzyme inhibitor/angiotensin II receptor blocker

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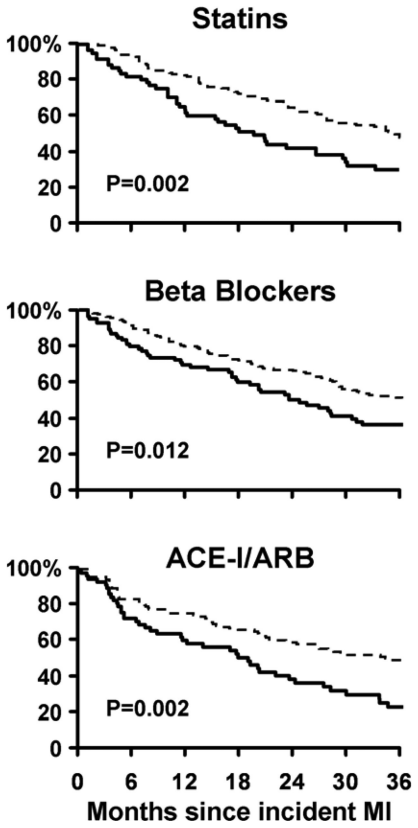

Figure 3. Medication Continuation by Enrollment in Cardiac Rehabilitation

Caption: Percentage of patients continuing medications by cardiac rehabilitation enrollment status over time for statins (top), beta blockers (middle) and ACE-I/ARB (bottom) are shown. Dashed lines represent patients who enrolled in cardiac rehabilitation while solid lines represent those who did not enroll in cardiac rehabilitation programs after MI.
MI= myocardial infarction; ACE-I/ARB= angiotensin converting enzyme inhibitor/ angiotensin II receptor blocker

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Table 1

Baseline Characteristics of MI Patients (n=292)

Age, yrs (SD)	64.5 (14.6)
Male, n(%)	184 (63)
Current smoker, n(%)	74 (25)
Diabetes, n(%)	64 (22)
Hypertension, n(%)	186 (64)
Hyperlipidemia, n(%)	194 (66)
Number of comorbidities, mean (SD)	2.5 (1.8)
ST segment elevation myocardial infarction, n(%)	86 (30)
Reperfusion, n(%)	205 (70)
Cardiac rehabilitation enrollment, n(%)	191 (65)
Medications at Discharge, n(%)	
Beta blockers	248 (84)
ACE Inhibitors/ ARB	180 (62)
Statins	219 (75)

SD= standard deviation; MI= myocardial infarction; ACE-I/ARB= angiotensin converting enzyme inhibitor/ angiotensin II receptor blocker

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Table 2

Predictors of Medication Discontinuation After Myocardial Infarction

	Statins (n=219)		Beta-blockers (n=248)		ACE Inhibitors/ARBs (n=180)	
Variable	**Hazard Ratio**	**95% CI**	**Hazard Ratio**	**95% CI**	**Hazard Ratio**	**95% CI**
Age (per year increase)	1.01	0.99-1.02	1.00	0.99-1.02	1.00	0.99-1.02
Male sex	0.82	0.58-1.17	1.01	0.72-1.40	0.84	0.57-1.24
Current Smoker	1.20	0.81-1.77	1.39	0.98-1.97	1.32	0.86-2.02
Received reperfusion or revascularization therapy	0.96	0.65-1.40	0.80	0.57-1.14	0.96	0.62-1.49
Enrolled in cardiac rehabilitation program	**0.66**	**0.45-0.92**	**0.70**	**0.49-0.98**	0.70	0.45-1.10
[a]Number of comorbidities	1.04	0.93-1.16	1.00	0.90-1.11	1.00	0.88-1.13

ACE-I/ARB= angiotensin converting enzyme inhibitor/ angiotensin II receptor blocker

[a]Determined from comorbidities used to calculate the Charlson comorbidity index