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Beta-blocker initiation and adherence after hospitalization for acute myocardial infarction

Running title: POST-AMI BETA-BLOCKER USE

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INTRODUCTION

Long-term use of beta-blockers after acute myocardial infarction (AMI) may reduce total mortality by as much as 26% [1]. Given the high incidence of AMI, it has been estimated that if all AMI survivors initiated and continued beta-blocker therapy for 20 years in the US alone, as many as 4,300 fewer deaths from chronic heart disease and 3,500 fewer repeat AMIs would occur in the United States [2].

Guidelines from the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology recommend use of beta-blockers in AMI patients without contraindications to such treatment [3-5]. However, post-AMI beta-blocker therapy is often underutilized [6-10]. Only 61% of patients who were candidates for post-AMI beta-blocker therapy actually initiated it in British Columbia, Canada, between 2001 and 2004 [9]. Furthermore, post-AMI beta-blockade is maximally effective only when patients adhere to the therapy and persist on it over the long-term [11]. However, observed adherence to and persistence with post-AMI beta-blocker therapy has also been low among those who initiate such therapy [12].

Little is known about recent patterns and predictors of post-AMI beta-blocker initiation [13] and recent trends in adherence to such therapy. Most studies currently available in the medical literature have examined patterns and predictors of beta-blocker therapy only up to 2004 and most of this evidence is from North America. Drug prescribing and utilization patterns can vary widely between countries and also within countries over time [14,15]. Thus, we sought to: (1) estimate the proportion of patients without contraindications who initiated beta-blocker therapy

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after AMI in Regione Emilia-Romagna (RER), Italy; (2) examine predictors, including patient and clinical characteristics and use of alternative medications, of beta-blocker initiation after AMI; and (3) estimate patient adherence to beta-blocker therapy after AMI using data from 2003 to 2008.

METHODS

Data source

We used the healthcare database from RER, comprising all of the approximately 4 million RER residents over the period 2003 to 2008. This database captures health service utilization information for the entire region, including hospital discharge abstract data, such as diagnosis and procedure codes, and outpatient prescription drug dispensing data. Individuals can be linked across data files with anonymous patient identifiers and can be followed longitudinally. This study complies with the Declaration of Helsinki and was approved by the Institutional Review Board of Thomas Jefferson University, Philadelphia, PA.

Cohort identification

We identified a cohort of patients with AMI comprising all RER residents aged 35 and older discharged alive from a regional hospital between January 1, 2004 and December 31, 2007 with a primary diagnosis of AMI (ICD-9 codes 410.x1) [16]. The index AMI admission for each patient was defined as the first AMI admission identified in the study period. We excluded patients discharged alive but whose length of stay for the index AMI admission was less than 3 days, as recorded AMI codes may have been for rule-out purposes in these cases [16,17].

Patients were also excluded if they died within 30 days of discharge to ensure a minimum time window for measuring beta-blockers use in the outpatient setting.

Patients were also excluded if they had absolute or relative contraindications to beta-blockers. Specifically, based on primary and secondary inpatient diagnoses in the year prior to index hospitalization, we excluded those with hypotension, heart block > 1 degree, sinus bradycardia, chronic obstructive pulmonary disease, or peripheral vascular disease. Patients with asthma were also excluded and were identified as those with a prescription record for inhaled corticosteroids in the 6 months prior to the index hospitalization or those with a primary or secondary hospital discharge diagnosis of asthma in year prior to the index AMI admission. Patients with type 1 diabetes mellitus, defined as those who had received insulin in the 6 months prior to or 3 months following the index AMI admission, were also excluded [17].

Covariates

Potential predictors of beta-blocker initiation were identified from inpatient data and prescription drug dispensing data in the year preceding index hospitalization – as early as the beginning of 2003 (a detailed list of ICD-9-CM codes and of Anatomical Therapeutic Chemical (ATC) classification system codes are available from the authors). We retrieved demographic information, including age, gender, and geographic location. We also collected information on cardiovascular health services use, including hospital admissions with primary diagnoses of angina, ischemic heart disease, congestive heart failure, and other cardiovascular diseases, as well as use of specific medications for cardiovascular conditions, including digoxin, angiotensin-converting enzyme (ACE) inhibitors, nitrates, beta-blockers, calcium channel blockers, and

angiotensin II receptor blockers (ARBs) [18]. Comorbidities were ascertained from non-cardiac

hospital admissions with primary diagnoses for other conditions that may increase mortality risk

[18]. We also used the Chronic Condition Drug Group (CCDG), a prescription drug-based

comorbidity index [19]. CCDGs were developed in the same RER database and have been

applied in other published studies [14,15,20]. Also, we computed the number of different drug

products filled in the 6 months before hospitalization as a proxy for health status [21]. Finally,

we constructed indicator variables for intensity of the in-hospital stay, including length of stay,

receipt of invasive cardiac procedures, and whether the patient received specialized care defined

as spending at least part of their stay in the cardiac surgery, intensive care, cardiology, or critical

care units.

Outcome measures and statistical analysis

We estimated the proportion of patients in the eligible cohort with at least one record of a

dispensing for a beta-blocker within 90 days after discharge from the index hospitalization. We

conducted a logistic regression analysis to identify which factors were independent predictors of

beta-blocker initiation in this cohort. Dichotomous post-AMI beta-blocker use was the

dependent variable in the model. All other covariates described above, including demographics,

comorbid conditions, and cardiovascular health services use, were entered into the model

simultaneously as independent variables to identify which factors were associated with beta-

blocker use while controlling for all other factors in the model. Odds ratios (ORs) and their 95%

confidence intervals were estimated for the association between beta-blocker initiation and each

of the independent variables. All analyses were conducted using SAS (version 9.1, Cary, NC).

Among cohort members with at least one prescription for a post-AMI beta-blocker, we estimated the proportion of days covered (PDC), or medication possession ratio, for beta-blocker therapy at 6 and 12 months from the first beta-blocker prescription dispensed. This interval-based PDC is a commonly used measure of drug availability and is a function of both adherence to (i.e. patient takes prescribed medication according to schedule) and persistence with (i.e. patient continues to take therapy) drug therapy over a defined time interval [22,23]. To estimate the 6- and 12-month PDCs, we first computed the number of days covered by beta-blockers within each time period of interest as the total number of Defined Daily Doses (DDDs) for any type of beta-blocker prescribed to each individual [22,24]. The DDD is a technical unit of measurement, used by the World Health Organization, which reflects the average adult dose used for the main indication as reflected by the Anatomical Therapeutic Chemical (ATC) classification system code [25]. We then divided the number of days covered by beta-blockers by 180 and 360 for the 6- and 12-month estimate, respectively, and multiplied by 100 to arrive at the estimated PDC. We excluded patients who died within 6 and 12 months after the index AMI, from each time interval, respectively. We used *a priori* PDC cutoffs of ≥80%, 50% to <80%, and <50% to classify patients as adherent, moderately adherent, and non-adherent, respectively [6]. We also calculated the mean 6- and 12-month PDC among initiators stratified by year of hospitalization and performed a Cochran-Armitage test for trend over time in the proportion of initiators who were adherent.

RESULTS

Study Cohort

We identified 28,001 patients who met the cohort eligibility criteria. Of these, 3,634 (13%) were

excluded because they had one or more contraindications to beta-blockers. Thus, the final study

cohort comprised 24,367 eligible patients hospitalized for AMI in RER between 2004 and 2007

(Table 1). Selected demographic and clinical information as well as factors related to the index

hospitalization are reported in Table 1, and are fully reported in the online supplement. Of the

eligible cohort, 16,383 (67%) received at least one outpatient dispensing for a beta-blocker in the

90 days after discharge from the index hospitalization (Table 1). Propranolol (61%) was the

most commonly dispensed index beta-blocker, followed by bisoprolol (19%), carvedilol (16%),

and atenolol (3%).

Following a slight increase in proportion of beta-blocker initiators between 2004 and 2005, the

proportion remained relatively unchanged between 2005 and 2007 (Figure 1). In general, those

who initiated beta-blockers were younger and appeared healthier than those who did not. For

example, beta-blocker initiators were hospitalized less often and had fewer comorbid conditions

in the year preceding index hospitalization as compared to patients who did not initiate beta-

blockers after discharge. Furthermore, those who initiated beta-blockers were more likely to

have also received specialized inpatient care and were more likely to have undergone invasive

cardiac procedures (Table 1 and online supplement).

Predictors of beta-blocker use

Table 2 presents the results of the multivariable logistic regression model examining independent

predictors of post-AMI beta-blocker initiation (see online supplement for full results). Adjusted

for other covariates in the model, the odds of initiating a post-AMI beta-blocker decreased

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monotonically with increasing age (Table 2). Undergoing coronary artery bypass graft (CABG) surgery (OR, 2.37; 95% CI, 2.00-2.81), percutaneous transluminal coronary angioplasty (PTCA; OR, 1.42; 95% CI, 1.31-1.54), and cardiac catheterization (OR, 1.14; 95% CI, 1.11-1.32) remained strong predictors of initiating post-AMI beta-blocker therapy (Table 2). Use of certain types of drugs for cardiovascular conditions in the 6 months leading up to index hospitalization were also strong predictors of beta-blocker use after discharge, including use of ACE-inhibitors (OR, 1.19; 1.11-1.28), ARBs (OR, 1.15; 95% CI, 1.05-1.26) and beta-blockers (OR, 1.81; 95% CI, 1.67-1.96).

Adherence to beta-blocker therapy

Within the first 6 months after discharge, 513 (3.1%) subjects who received post-AMI beta-blockers died and were excluded from both the 6-month PDC estimation. A total of 961 (5.9%) of beta-blocker initiators died during the follow-up year and were excluded from the 12-month PDC estimation. Monotonic decreases in mean 6- and 12-month PDC estimates were observed between 2004 and 2007. Mean 6-month PDC was 64.5% in 2004, 62.2% in 2005, 60.3% in 2006, and 58.4% in 2007. Mean 12-month PDC was 59.3% in 2004, 57.3% in 2005, 55.2% in 2006, and 53.8% in 2007. The proportion of beta-blocker users who were adherent at 6 months following therapy initiation and at 12 months following initiation (Figure 2) also decreased over time (*p* for trend <0.001 for both 6- and 12-month PDC).

DISCUSSION

Among patients identified as being eligible for beta-blocker treatment following AMI hospitalization in RER, only two-thirds initiated such therapy between 2004 and 2007, despite

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compelling evidence of substantial reductions in morbidity and mortality associated with such treatment. This proportion is within the range of estimates previously observed in other countries. For example, in Canada, 61% of patients initiated post-AMI beta-blocker therapy in British Columbia, between 2001 and 2004 [9] and 77% were initiators in Ontario over the same period [6]. The 67% that we observed was a substantial improvement over the 9% to 31% uptake observed by Avanzini and colleagues in Italy in 1983-1994 [13].

Adherence to and persistence with beta-blocker therapy in the 6 and 12 months following treatment initiation was low, and much lower than that observed in other studies [6,12,26]. We also observed that the mean PDC and the proportion of patients classified as adherent decreased over time, even though the proportion of patients surviving AMI hospitalization who initiated beta-blocker therapy was largely unchanged during this period. These findings are in contrast with observations from the US and Canada which indicate that adherence with beta-blocker therapy was on the rise between the 1990s and 2003 [12,26]. A particular strength of our study is that it uses recent data. Further investigation in other regions and countries using recent data is required to understand if our observed decrease in adherence is specific to RER, or to Italy, or if trends in other countries also regressed after 2003.

Several demographic variables, frailty and comorbidity indicators, and factors related to index hospitalization were identified as independent predictors of post-AMI beta-blocker use. Consistent with a similar population-based study in Finland [27], we found that beta-blocker initiation was inversely associated with age. In general, older individuals and those with conditions indicating illness and frailty were less likely to initiate beta-blockers after AMI. It is

possible that prescribing of drugs for secondary prevention may often be avoided in patients with poor prognoses, based on the belief that preventive strategies may confer little benefit while adding the burden of an additional treatment in these patients. Providers may also be reluctant to prescribe beta-blockers to older patients because of concern of adverse events.

An important limitation of our study is that we were unable to distinguish between patients who did not receive a beta-blocker prescription from a provider following AMI hospitalization and those that did receive a prescription but never filled it (so-called primary non-adherence) [28]. Among post-AMI patients in other countries, it has been estimated that up to 1 in 5 patients exhibit primary non-adherence [28,29]. Thus, a substantial proportion of the 33% of patients that we identified as non-initiators may be patients who received a beta-blocker prescription but did not fill it. Whether due to suboptimal prescribing or to primary non-adherence, it appears that many patients in RER who could benefit from beta-blocker therapy are not using it. Indeed, results from several studies suggest that older patients benefit considerably from beta-blockade [18,30]. Other studies have also found that the patients who are least likely to receive post-AMI beta-blocker therapy may be those in whom beta-blockade confers the greatest benefit [8].

We found that patients who underwent invasive cardiac procedures during hospitalization for AMI (i.e. CABG, PTCA, and cardiac catheterization) were more likely to initiate beta-blocker therapy after discharge as compared to those patients who did not undergo such procedures. Consistent with prescribing decisions based on prognosis, this observation may reflect the notion that those who receive invasive procedure are those expected to have better prognoses and those that are expected to have better prognoses are those who are more likely to receive post-

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discharge beta-blocker therapy. Alternatively, this finding may suggest that hospitals with the capacity and expertise to provide invasive cardiac treatment for AMI are also more likely to provide appropriate medical management, such as post-AMI beta-blocker treatment. On a patient-level, this finding could reflect the notion that patients who consent to invasive procedures are more likely to initiate subsequent preventive health measures. Regardless of the explanation, this finding is in stark contrast with results from other studies. One US-based study found that patients receiving intensive in-hospital treatment, measured as the receipt of cardiac catheterization within 30 days of AMI, were less likely to receive post-AMI beta-blocker therapy [31]. In another study among US Medicare patients with AMI, geographic regions where invasive procedures are more common were less likely to provide beta-blocker therapy to their patients [32]. Additional research in RER should focus on the relation between post-AMI beta-blocker use and geographic provision of intensive cardiac care in the region (i.e. hub and spoke [33]).

Given the solid scientific foundation for post-AMI beta-blockade and the low concordance with such evidence-based care that we observed in routine practice, health policy actions may be warranted. Quality improvement initiatives, such as pay-per-performance programs, could be established to encourage appropriate beta-blocker prescribing for eligible patients in accordance with guidelines. In addition, educational programs targeting AMI survivors could improve patient adherence to appropriate beta-blocker therapy. Such patient-directed activities could focus on those individuals who are least likely to receive appropriate care but in whom the benefits of such care confer the greatest benefit, such as older individuals.

Our study has several additional limitations. First, it is not possible to accurately identify those patients in whom beta-blockers are ineffective or not tolerated using administrative claims data and sufficient information to identify all patients with contraindications to therapy may be limited. For example, we could not identify patients who may have received beta-blockers in the hospital, were intolerant, and subsequently discontinued therapy prior to discharge. Furthermore, we relied on definitions of contraindications used by previous investigators and we were unable to assess their validity in the RER database. Thus, due to misclassification, we may have included in our cohort patients with relative contraindications that are not captured in administrative healthcare data. Also, the regional policy of directly distributing medications to patients from hospital pharmacies both at discharge and for outpatient treatment could have resulted in a slight underestimate of post-AMI beta-blocker use since these data are not captured at an individual level in the RER database. Finally, we used DDDs to estimate a proxy of days supply in order to derive the PDC. However, DDDs are fixed units of measurement and may not always reflect prescribed daily doses for individual patients [25]. As a result, DDDs provide only a rough estimate of utilization. It is possible that some PDC misclassification occurred, but this is not likely to have substantially affected the results.

In conclusion, despite the well-documented benefits of beta-blockade after AMI, beta-blocker therapy remained underutilized in RER. Utilization was less likely among older individuals and among those with indicators of frailty, such as multiple and various comorbid conditions, even though these patients may benefit from post-AMI beta-blockade. Among those who did initiate post-AMI beta-blocker treatment, adherence to and persistence with such therapy was also low and decreased over time in RER between 2004 and 2007.

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LEGENDS

Figure 1. Proportion of patients surviving hospitalization for acute myocardial infarction with post-hospitalization beta-blocker initiation, 2004-2007

Figure 2. Proportion of patients initiating beta-blocker therapy following hospitalization for acute myocardial infarction who were adherent, moderately adherent, and non-adherent within the first 6 months of treatment (Panel A) and within the first year of treatment (Panel B), 2004-2007

Table 1. Selected demographics and characteristics of acute myocardial infarction hospitalization survivors in Regione Emilia-Romagna, 2004-2007*

	All patients hospitalized for AMI (n=24,367)	Beta-blocker initiators (n=16,383)	Beta-blocker non-initiators (n=7,984)
Age group, n (%)			
<55	3,135 (12.9)	2,347 (14.3)	788 (9.9)
55-64	4,334 (17.8)	3,303 (20.2)	1,041 (13.0)
65-74	6,019 (24.7)	4,370 (26.7)	1,649 (20.7)
75-84	7,394 (30.3)	4,716 (28.8)	2,678 (33.5)
85+	3,475 (14.3)	1,647 (10.1)	1,828 (22.9)
Male, n (%)	15,584 (64.0)	10,845 (66.2)	4,739 (59.4)
Primary or secondary diagnoses in prior year, n (%)			
Congestive heart failure	793 (3.2)	384 (2.3)	409 (5.1)
Angina pectoris	372 (1.5)	262 (1.6)	110 (1.4)
Other ischemic conditions	665 (2.7)	458 (2.9)	207 (2.6)
Other cardiovascular diseases	2,447 (10.0)	1,426 (8.7)	1,021 (12.8)
Pre-hospitalization medications, n (%)			
Digoxin	982 (4.0)	536 (3.3)	446 (5.6)
ACE-inhibitors	7,837 (32.2)	5,348 (32.6)	2,489 (31.2)
Nitrates	4,732 (19.4)	3,062 (18.7)	1,670 (20.9)
Beta-blockers	5,710 (23.4)	4,385 (26.8)	1,325 (16.6)

CCBs	5,917 (24.3)	4,036 (24.6)	1,881 (23.6)
ARBs	3,636 (14.9)	2,556 (15.6)	1,080 (13.5)
Secondary diagnoses with high mortality risk at index admission, n (%)			
Cancer	1,354 (5.6)	797 (4.9)	557 (7.0)
Renal disease	827 (3.4)	363 (2.2)	464 (5.8)
Pneumonia	3,611 (14.8)	1,974 (12.0)	1,637 (20.5)
Cerebrovascular disease	15,980 (65.6)	10,424 (63.6)	5,556 (69.6)
Any one of high-risk secondary diagnoses	16,439 (67.5)	10,703 (65.3)	5,736 (71.8)
CCDG score in prior year, n (%)			
0-1	11,346 (46.6)	7,687 (46.9)	3,659 (45.8)
2-3	9,804 (40.2)	6,628 (40.5)	3,176 (39.8)
4+	3,217 (13.2)	2,068 (12.6)	1,149 (14.4)
Index hospitalization length of stay, mean±SD	11.1±11.8	10.3±10.4	12.7±14.1
CABG during index hospitalization, n (%)	1,082 (4.4)	838 (5.1)	244 (3.1)
PTCA during index hospitalization, n (%)	13,784 (56.6)	10,250 (62.6)	3,534 (44.3)
Cardiac catheterization during index hospitalization, n (%)	17,364 (71.3)	12,721 (77.6)	4,643 (58.2)

SD=standard deviation; ACE=angiotensin-converting enzyme; CCBs=calcium channel blockers; ARBs=angiotensin II receptor blockers; CCDG=chronic condition drug groups; CABG=coronary artery bypass graft; PTCA=percutaneous transluminal coronary angioplasty

* See online appendix for full list of baseline demographics and patient characteristics

Table 2. Selected independent predictors of beta-blocker initiation following acute myocardial infarction hospitalization discharge in Regione Emilia-Romagna, 2004-2007*

Variable	Odds Ratio	95% Confidence Interval
Age group		
<55	Referent	-
55-64	0.97	0.87-1.09
65-74	0.82	0.73-0.91
75-84	0.66	0.59-0.73
85+	0.46	0.41-0.53
Sex		
Female	Referent	-
Male	0.95	0.89-1.01
Primary or secondary diagnoses in prior year		
Congestive heart failure	0.87	0.71-1.08
Angina pectoris	1.27	0.99-1.62
Other ischemic conditions	1.26	0.99-1.61
Other cardiovascular diseases	0.95	0.84-1.07
Pre-hospitalization medications		
Digoxin	0.97	0.84-1.12
ACE-inhibitors	1.19	1.11-1.28
Nitrates	1.00	0.92-1.09
Beta-blockers	1.81	1.67-1.96
CCBs	1.09	1.01-1.17

ARBs	1.15	1.05-1.26
Secondary diagnoses with high mortality risk at index admission		
Cancer	0.94	0.83-1.06
Renal Disease	0.66	0.56-0.76
Pneumonia	0.88	0.81-0.96
Cerebrovascular disease	0.93	0.76-1.15
Any one of high-risk secondary diagnoses	1.06	0.85-1.31
CCDG score in prior year		
0-1	Referent	-
2-3	1.02	0.94-1.11
4+	1.02	0.91-1.15
Index hospitalization length of stay (for every 5-day increase)	0.96	0.95-0.97
CABG during index hospitalization	2.37	2.00-2.81
PTCA during index hospitalization	1.42	1.31-1.54
Cardiac catheterization during index hospitalization	1.21	1.11-1.32

SD=standard deviation; ACE=angiotensin-converting enzyme; CCBs=calcium channel blockers;

ARBs=angiotensin II receptor blockers; CCDG=chronic condition drug groups; CABG=coronary artery

bypass graft; PTCA=percutaneous transluminal coronary angioplasty

* See online appendix for full list of predictors of beta-blocker initiation