

Utilization of Beta Blockers Post-Myocardial Infarction

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SUMMARY

Beta blockers provide both morbidity and mortality benefits for post-myocardial infarction (MI) patients. Despite this, beta blockers are still often underused or used at suboptimal dosages. This was a retrospective observational study with the objectives of estimating the proportion of post-MI patients who are receiving beta-blocker therapy in University Malaya Medical Centre (UMMC), assessing the number of them receiving beta blockers at optimal dosages and determining the factors associated with beta-blocker prescribing post-MI.

Of 315 patient case notes reviewed, 77.5% were prescribed beta blockers. However, dosages were optimized in only 39.3% of patients. Reasons for not optimizing the dosages were typically not due to the presence of contraindications to beta blockers. Elderly (> 65 years old), ejection fraction (EF) < 40%, a history of cerebrovascular accident (CVA) or mild asthma, use of calcium channel blocker (CCB), digoxin or anti-asthmatic agents were all significantly associated with a reduced rate of beta-blocker prescribing post-MI. More effort should be placed in improving its use in specific patient populations. Initiatives to optimize the dosage of beta blockers to recommended dosages that matched those in clinical trials with proven mortality benefits will also need to be intensified.

KEY WORDS:

Beta-blockers; BB; post-myocardial infarction; post-MI

INTRODUCTION

Myocardial infarction (MI) is a major health problem, with relatively high rates of morbidity and mortality¹. Based on evidence from numerous large, randomized placebo-controlled trials, beta blockers are strongly recommended in all post-MI patients provided that they have no specific contraindications to this drug^{2,3}. Beta blockers have been demonstrated to improve the long-term prognosis post-MI in terms of mortality and sudden cardiac death^{3,4}. Additionally, beta blockers administered post-MI have been shown to decrease reinfarction rates^{4,5} and infarct size^{6,7}, prevent ischemic complications³, and reduce the incidence of intracerebral hemorrhage⁸.

Despite strong evidence from landmark clinical trials on the long-term survival benefits of beta-blocker use post-MI, beta blockers are still underused^{4,9,10,11,12}. A systematic review with meta regression analysis of beta-blockade after MI found that beta blockers were used in less than half of eligible patients¹³.

Studies have also shown that although beta blockers were given after MI, the prescribed dosages were not at dosages that matched those in clinical trials with proven mortality benefits^{2,4}. Two studies have found that even patients who were 65-75 years benefited from full-dosage of beta blockers^{14,15}. Therefore, not only should these patients receive beta-blocker therapy, their dosages should also be optimized to equivalent effective dosages used in clinical trials.

Several studies have described various factors associated with beta-blocker underuse^{8,16,17}. These include diabetes mellitus, advanced age, calcium channel blocker use and other therapies. Ironically, some of these patient populations have been found to derive greater benefits when prescribed beta blockers than when not. For instance, patients with diabetes mellitus, which is an important risk factor for mortality after MI, have significantly lower mortality rates at 1-year when they received beta-blocker therapy compared to those who did not¹¹. Similarly, this study also found older patients had greater mortality benefits when prescribed beta blockers post-MI compared to those not receiving the drug. Other reasons that may contribute to beta-blocker underuse include the diagnosis of asthma, symptomatic heart failure, prescribers' concern of its side effects and women as demonstrated in various studies^{8,18}. The underuse of beta blockers among diabetics, asthmatics and patients with heart failure are likely due to continuing misconceptions that beta blockers should be avoided in these groups of patients although many recent studies have proven otherwise^{19,20,21,22}.

To our knowledge, there has not been any study published on the use of beta blockers post-MI in the local setting. Therefore, the aim of this study was¹ to assess the utilization of beta blockers post-MI in a large tertiary care hospital in Malaysia and² to determine the factors associated with beta-blocker prescribing. The findings of this study will be helpful to both clinicians and pharmacists in designing useful interventional strategies to optimize the standard of care delivered to post-MI patients.

MATERIALS AND METHODS

This was a retrospective observational study conducted in University Malaya Medical Centre (UMMC).

The sampling frame included patients admitted to UMMC with a history of MI diagnosed between 2002 and 2004, identified from their International Classification of Diseases, Tenth Revision (ICD-10) codes for the discharge diagnosis of MI; I21.0-I21.4, I21.9, I22.0, I22.1, I22.8, I22.9 and I25.2. The

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review of beta-blocker use post-MI was done after the release of the 2001 Malaysian Clinical Practice Guidelines (CPG) on acute MI (AMI) in mid-2001 to allow a sufficient period for information dissemination and for physicians to adopt to the new changes in prescribing recommendations since the landmark clinical trials for which we were assessing the optimal dosages were adopted by these guidelines. Patients who were diagnosed in the year 2005 were excluded, as a time period of 12-months had been chosen to assess patients for beta-blocker dosage optimization in this study.

A total of 1541 registration numbers (RN) were generated and a systematic sampling was conducted with every 4th patient chosen as a study sample. The targeted sample size was 385 patients. The calculated sample size (confidence level of 95%; CI of 5%; estimated proportion of 0.5) was 308 patients. Following the identification of 385 RN, the patients' medical records were subsequently reviewed to assess their eligibility in the study.

All patients with a history of MI, confirmed by the World Health Organization (WHO) criteria for MI diagnosis and who survived for at least 1 year were included. The confirmation based on the WHO criteria (2 out of 3: ischemic type chest pain; electrocardiogram (ECG) changes; raised cardiac markers)²⁹ was done according to the presenting parameters noted in the case notes. The presence of a Q wave on ECG tracings was required for patients with the diagnosis of an old MI prior to inclusion in the study.

We excluded patients with first-admission deaths, as these patients did not have the opportunity to receive beta-blocker therapy. Because of the difficulty to obtain complete medication records, patients who were transferred from other institutions were excluded. We also excluded patients with incomplete medical records and those who failed to follow up for a 12-months period in UMMC following MI because of the need to assess beta-blocker dosage optimization.

Patients' medical records that fulfilled the inclusion and exclusion criteria were reviewed for a period of 12 months following the diagnosis of MI.

Assessment of the presence of contraindications to beta blockers was based on the Malaysian CPG on AMI²³ which was the most current guideline available at the point of this study. These contraindications were considered valid reasons for post-MI patients not to be given beta-blocker therapy; bradycardia (< 60 beats/minute); systolic blood pressure < 100 mmHg; pulmonary congestion with crepitations beyond the bases; signs of peripheral hypoperfusion; atrioventricular block; severe chronic obstructive pulmonary disease (COPD) or asthma; and severe peripheral vascular disease (PVD).

Optimal dosages of beta blockers in this study constituted both the achievement of target effective doses or maximum tolerated doses. Target effective doses (Table I) were defined as doses used in landmark clinical trials, which have been shown to have mortality benefits and improved survival in post-MI patients⁴. Maximum tolerated doses were defined as doses at which post-MI patients began showing signs of

bradycardia or systolic hypotension². These patients were considered to have optimized dosages although their final doses had not reached the target effective doses recommended in landmark clinical trials.

The protocol of this study was approved by the UMMC Medical Ethics Committee (Reference number: 472.31).

Data entry and statistical analyses were done using the Statistical Package for the Social Sciences version 12.0 software (SPSS Inc., Chicago IL, USA). Data were tabulated and presented in the graphical form using Microsoft Excel and Word. Descriptive statistics were used to present the proportion of patients receiving beta-blocker therapy post-MI. The assessment of significant patient characteristics associated with the use of beta blockers was done using bivariate analysis of chi-square (χ^2) or Fisher's Exact Test (FET) for discrete variables (age, ejection fraction, comorbidities, concurrent medications, and revascularization). A p value of < 0.05 was considered significant in this study.

RESULTS

Out of the 385 case notes reviewed, 315 patients met the inclusion criteria (Figure 1). Majority of patients were male (79.7%), Malay (36.2%) and \leq 65 years old (70.5%) with a mean \pm standard deviation (SD) age of 59.2 (\pm 12.3) years old.

37.8% of patients were thrombolysed with streptokinase and revascularization (percutaneous transluminal coronary angioplasty) with or without stenting or coronary artery bypass grafting surgery was performed in 168 (53.3%) patients.

Hypertension (61.9%) was found to be the commonest comorbidity among post-MI patients followed by diabetes (51.1%). Aspirin (94%) was the most frequently used concurrent medication followed by statins (90.2%).

Treatment with Beta Blockers Post-Myocardial Infarction

Two hundred and fifty three (80.3%) patients received oral beta-blocker therapy. However, 9 (3.6%) of them stopped therapy within 6-months due to contraindications. Thus, only 244 (77.5%) received beta-blocker therapy on a long-term basis. Atenolol was the most commonly prescribed agent at the end of the study period (n=100, 41%), followed by metoprolol (n=83, 34%), carvedilol (n=56, 23%) and bisoprolol (n=5, 2%).

Contraindications to beta-blocker therapy were present in 75 (23.8%) patients which were persistent throughout the study period. These included patients who did not receive beta blockers and those who tolerated the drug despite having contraindications to it (Table II).

The median duration to start beta-blocker therapy post-MI was one day. This assessment included all patients including those who subsequently stopped therapy within the study period as we were assessing the intention of physicians to start beta-blocker therapy. Of 253 patients who received beta-blocker therapy with the intention to treat, 93.3% received

Table I: Target Effective Doses Used in Landmark Clinical Trials

Beta Blocker	Route of Administration	Target Effective Dose	Clinical Trial
Metoprolol	Intravenous	15mg within 24 hours	MIAMI trial 1985 ⁷
	Oral	200mg daily	
Metoprolol	Intravenous	15mg	Hjalmarson et al. 1981 ³
	Oral	100mg twice a day	
Atenolol	Intravenous	5-10mg over 5 minutes	ISIS-1 trial 1988 ⁶
	Oral	100mg daily	
Propranolol	Oral	180-240mg daily	BHAT trial 1981 ²⁵
Carvedilol	Oral	25mg twice a day	CAPRICORN trial 2001 ¹⁹

MIAMI - metoprolol in acute myocardial infarction; ISIS-1 - first international study of infarct survival; BHAT - beta-blocker heart attack trial; CAPRICORN - carvedilol post infarction survival control in left ventricular dysfunction

Table II: Contraindications Present in the Study Population (N=75)

Contraindicationsa	Patient Received Beta-Blocker Therapy (Number)		n (%)
	Yes (n=39b)	No (n=36c)	
	Bradycardia (< 60 beats/minute)	15	
Systolic blood pressure < 100 mmHg	5	10 (3 stopped)	15 (20.0%)
Pulmonary congestion with crepitations beyond the bases, signifying active pulmonary oedema (APO)	12	4	16 (21.3%)
Signs of peripheral hypoperfusion	3	3 (1 stopped)	6 (8.0%)
AV block	1	2	3 (4.0%)
Severe COPD or asthma	3	10	13 (17.3%)
Severe PVD	0	2	2 (2.7%)

a Every patient had only a single contraindication

b Patients received beta-blocker therapy by the end of the 12-months study period (atenolol, metoprolol, carvedilol and bisoprolol) without any negative consequence

c No beta-blocker therapy given (including those who stopped the therapy within the study period; 6 with documented contraindications, 3 undocumented)

APO - active pulmonary oedema; AV - atrioventricular; COPD - chronic obstructive pulmonary disease; PVD - peripheral vascular disease

beta blockers during their first MI admission, 4.7% by 6-months and 2.0% by 12-months.

Dosage Optimization of Beta-Blocker Therapy

The assessment of optimal dosages of beta-blocker therapy post-MI excluded patients who stopped therapy within the study period and patients on bisoprolol, as the optimal dosage for this drug in post-MI patients had yet to be established in clinical trials at the point of this study. Of 239 patients assessed, 93.7% of patients started their therapy during the first MI admission, 10 (4.2%) by 6-months and 5 (2.1%) by 12-months.

The dosages of beta blockers received initially and at 12-months are shown in Figure 2. At the end of the study period, only 13% of patients had achieved their full target effective dose.

Only 94 (39.3% of 239) patients received either maximum tolerable or target effective doses of beta-blocker therapy. Figure 3 shows the number of patients achieving their optimal dosages at various time frames within the study period. Optimal beta blocker dosages were more often achieved in younger patients (<65 years) versus the elderly (>65 years), 75.5% vs. 24.5%, respectively.

Factors Associated With Beta-Blocker Prescribing

In the assessment of risk factors associated with the use of beta blockers post-MI, patients with clear contraindications to beta blockers were excluded (N=75) to prevent confounding. From the remaining 240 patients reviewed, 205 patients received beta blockers post-MI.

Elderly patients (aged > 65) were significantly associated with a lower rate of beta-blocker prescribing, $\chi^2(df=1, N=240) = 6.10, p=0.01$. Meanwhile, there was no significant relationship found between gender and beta-blocker use post-MI, $\chi^2(df=1, N=240) = 0.01, p=0.9$. Patients with EF value < 40% were less likely to be treated with beta blockers compared to those with EF value $\geq 40\%$, $p=0.02$, FET.

Comorbid variables that was significantly associated with a failure to prescribe beta-blocker therapy were CVA, which was inclusive of stroke and transient ischemic attack (TIA) ($p=0.001$); and mild asthma ($p=0.01$).

The use of CCB, digoxin and anti-asthmatic agents were important predictors of failure to prescribe beta blockers to post-MI patients without contraindications to beta blockers. Patients who were on CCB or digoxin were less likely to be treated with beta blockers compared to those without, $\chi^2(df=1, N=240) = 4.99, p=0.03$ and $p=0.02$, FET, respectively. Among patients who received concurrent anti-asthmatic agents, 75% (n=3) did not receive beta-blocker therapy, $p=0.01$, FET. Meanwhile, use of clopidogrel was found to be significantly associated with the use of beta-blocker therapy, $\chi^2(df=1, N=240) = 4.04, p=0.04$.

Patients who had undergone revascularization were also found to more likely have received beta-blocker therapy post-MI compared to those who had not undergone revascularization. 89.9% vs. 80.2%, $\chi^2(df=1, N=240) = 4.55, p=0.03$.

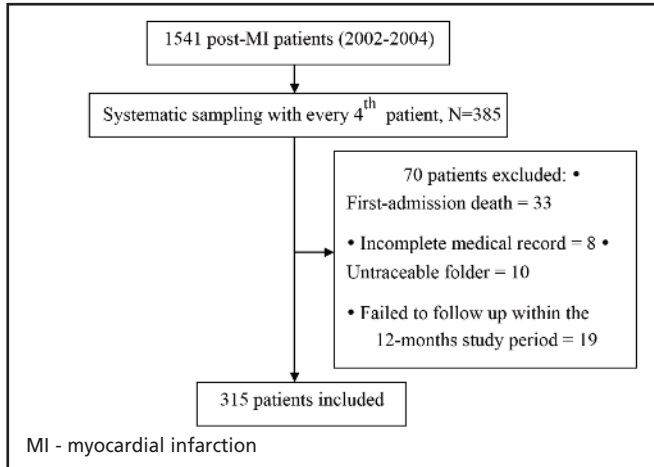


Fig. 1: Flowchart of Patient Disposition.

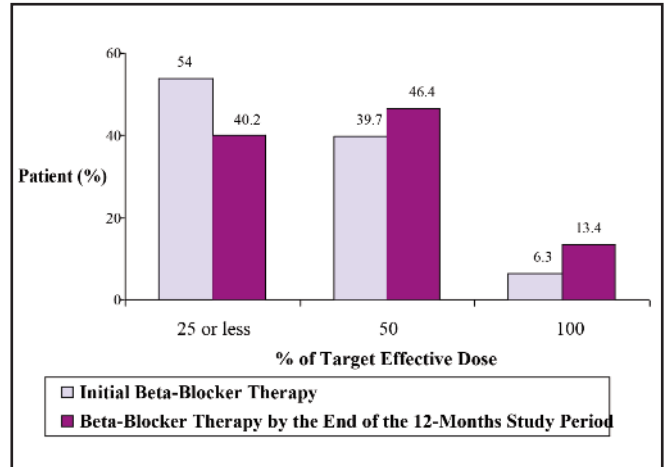


Fig. 2: The Dosage of Beta Blockers Received (N=239).

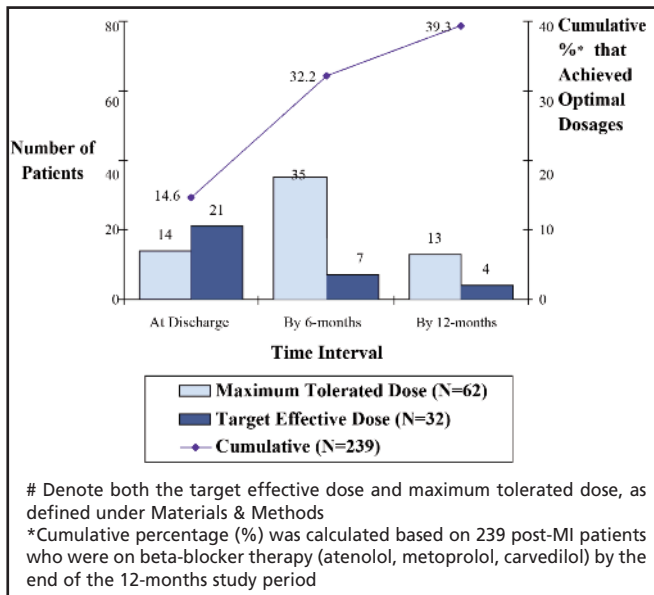


Fig. 3: Optimal Dosages[†] of Beta-Blocker Therapy Achieved

DISCUSSION

Treatment with Beta Blockers Post-Myocardial Infarction

We found a high rate of beta-blocker prescribing (77.5%) post-MI in our institution. In contrast, other studies have reported lower rates of beta-blocker use ranging from 34.0%¹¹ to 60.2%²⁴. These other studies assessed beta-blocker use soon after an MI episode, either during hospitalization²⁴ or at discharge¹¹ while our study assessed the use of beta blockers over a 12-months period allowing higher chances for physicians to initiate therapy.

Only a minority of post-MI patients had clear contraindications to beta blockers. Such patients comprised only 23.8% of our study group, which is slightly more compared to rates reported in other studies (18%)^{4,25}. This may have been due to minor differences in the assessment for contraindications to beta blockers. For instance, some studies defined bradycardia as heart rates of < 50 beats/minute whereas we used cut-offs of < 60 beats/minute as suggested in the Malaysian CPG on AMI²³.

In this study, it was surprising to find that 16% of patients received beta-blocker therapy despite clear contraindications to the drug. All of these patients tolerated beta blockers without exacerbations of their clinical conditions albeit at maximum tolerated doses. This is not inconsistent with previous published reports²².

Early use of beta blockers in post-MI patients has shown to reduce mortality rates and decrease infarct size²⁶. In this study, we found that the majority of patients who were given beta-blocker therapy received them during their first MI admission. Prior studies have reported varying rates of early beta-blocker initiation, ranging from 34% to 60%^{24,11}. We were however, unable to assess the mortality benefits of early vs. late therapy initiation in this cohort given the short follow up duration.

Dosage Optimization of Beta-Blocker Therapy

Though we found high rates of beta blocker prescribing post-MI, most patients received suboptimal doses. The majority of patients received 50% or less than the dosages recommended in clinical trials, with only 39.3% of patients receiving optimal dosages. We also found that the failure to increase dosages during the study period were not typically due to the presence of contraindications. Patients who received suboptimal dosages may not have received maximum benefits from their beta-blocker therapy¹⁶. Studies have found beta blockers reduced the risk of repeat hospitalizations²⁷. In our setting, we found more than 70% of patients studied had at least one cardiovascular-related readmission. We speculate that this high re-admission rate could be due to suboptimal beta-blocker dosages received but no formal analysis was done to prove this.

We also found that optimal dosages were more likely achieved in young vs. elderly patients in our cohort. Dosages were likely kept low in elderly patients possibly due to concerns of adverse effects in this population. A retrospective study assessing the 1-year survival for elderly patients receiving beta-blocker therapy post-MI has found that these patients derived more benefits with lower beta-blocker dosages²⁸. Randomized clinical trials are needed to determine the optimal dosages of beta-blocker therapy for elderly post-MI patients²⁹.

Factors Associated With Beta-Blocker Prescribing

Many patients not receiving beta-blocker therapy were elderly patients, as has been shown in other studies^{2,11,17,18,28,29,30}. This could possibly be because elderly patients are more susceptible to adverse drug effects³¹; therefore they may be a particularly undertreated group. Subgroup analysis of most prospective trials does not suggest a decreased benefit from beta-blockade with increasing age^{3,25}. Therefore, with close follow-up, advanced age should not be viewed as a contraindication to beta blockers.

Our results were similar to results previously published⁴, whereby EF < 40%, which usually warrants the diagnosis of heart failure, significantly predicted failure to prescribe beta blockers. The patients receiving beta blockers was 93.1% among those with EF ≥ 40% vs. 80.4% among patients with EF < 40%. However, the numerical percentage of patients with EF < 40% or heart failure who received beta blockers was much higher compared to two studies which ranged from 12.4%¹¹ to 21.0%⁴. It should be noted that at one point beta blockers were contraindicated in heart failure and that these studies were performed relatively soon after the change in prescribing recommendations³². With time, there have been more trials, guidelines and studies supporting the utilization of beta blockers in these patients, thus the percentage of its use may have increased in line with more evidence.

Patients with a history of CVA were less likely to receive beta-blocker therapy post-MI, compared to those without a history of CVA. Reasons for not starting beta blockers in these patients were not entirely clear and further studies need to be performed to understand the underlying reasons for this.

Our results were consistent with other studies^{11,33} which have found that post-MI patients with mild asthma are not frequently prescribed beta blockers. Reasons may be largely because of physicians' concerns of disease exacerbation with beta-blocker use. Patients with mild asthma with or without beta-agonists have been shown to derive benefits from beta-blocker therapy²¹, which was found to be associated with lower death rates^{10,11,34}. Our findings highlight the need to prescribe a beta blocker if the patient can tolerate it.

Therefore, every effort should be made to determine the severity of the patient's pulmonary condition before therapy is begun.

Previous studies have reported that diabetes was associated with the underuse of beta-blocker therapy post-MI^{18,35}. However in this study, we found no significant difference in beta-blocker use between diabetics and non-diabetics. The reason could be possibly due to the different guidelines consulted in assessing contraindications to beta blockers. The 1999 ACC/AHA guidelines³⁴ listed diabetes mellitus as a relative contraindication to beta-blocker use; however the Malaysian CPG on AMI²³ does not. Therefore, physicians in western countries who treat patients based on the ACC/AHA guidelines have a tendency not to start beta-blocker therapy in diabetic patients, which was not seen in our study population.

The use of CCB or digoxin was significantly associated with a less likelihood to prescribe beta blockers post-MI without clear

contraindications. Similar findings have been reported in other studies^{12,17,36}. This could be due to the fact that both CCB and digoxin are heart rate-modulating agents³⁷. Physicians may have a tendency to avoid the use of these agents concurrently with beta-blocker therapy, as they all have negative chronotropic effects. Given the strong evidence of mortality benefits provided by beta-blockers post-MI, beta blockers should be given priority over the use of CCB and digoxin in post-MI patients.

Concurrent anti-asthmatics (beta agonists) were significantly associated with the reduced use of beta-blockers post-MI. These findings may be confounded by the diagnosis of mild COPD or asthma, which have previously described as a factor associated with underuse of beta blockers post-MI. Therefore, increasing its use in post-MI patients with these conditions is essential as it would improve the care and outcomes of these patients²¹.

We found that, after excluding patients with contraindications to beta blockers, those who have undergone revascularization or the use of concurrent clopidogrel were significantly more likely to receive beta blockers post-MI. The use of clopidogrel may be confounded by revascularization. This could be probably because revascularization is usually performed in post-MI patients with more severe conditions and antiplatelet agent like clopidogrel is commonly prescribed after these procedures³⁷. Patients with severe conditions are more likely to receive more drugs and have their therapy optimized. Therefore, this could likely create the occurrence of higher rate of beta-blocker prescribing in these patients.

This study has several limitations. Firstly, the retrospective study design led to the reliance of data collected by others that could have been documented erroneously. Furthermore, post-MI patients with undocumented reasons for not receiving beta blockers could not be further clarified due to this study design. Secondly, our reliance on using the ICD-10 codes for patient selection may have unintentionally led to exclusion of the patients due to coding errors. Lastly, the strength of the factors discussed as predictors of beta-blocker utilization need to be further assessed using multivariate statistical models to identify independent predictors. This method of analysis was however beyond the scope of this study.

CONCLUSION

We found a high rate of beta-blocker prescribing in post-MI patients in UMMC. However, beta blocker dosages prescribed in these patients were often suboptimal and lower than the dosages recommended in clinical trials with proven mortality benefits. Reasons for not increasing the dosages within the study period were typically not due to the presence of contraindications to beta blockers. Factors associated with beta blocker underuse included elderly patients, patients with EF < 40%, history of CVA, mild asthma and diabetics. Additionally, patients receiving CCB, digoxin and anti-asthmatics were also less likely to receive beta-blocker therapy post MI. Beta-blocker therapy has been continuously shown to provide mortality benefits in post-MI patients even at lower dosages, thus the physicians should be encouraged

to prescribe beta blockers to eligible patients at their tolerated dosages.

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