Published in final edited form as:

Am Heart J. 2016 April ; 174: 37–42. doi:10.1016/j.ahj.2015.11.018.

Initiation of Beta-Blocker Therapy and Depression After Acute Myocardial Infarction

Anil M. Ranchord, MD*, John A. Spertus, MD, MPH^{*,†}, Donna M. Buchanan, PhD^{*,†}, Kensey L. Gosch, MS*, and Paul S. Chan, MD, MSc^{*,†}

* Saint Luke's Mid America Heart Institute, Kansas City, MO

† University of Missouri - Kansas City, Kansas City, MO

Abstract

Introduction—Although beta (β)-blockers reduce mortality after acute myocardial infarction (AMI), early reports linking β -blocker use with subsequent depression have potentially limited their use in vulnerable patients. We sought to provide empirical evidence to support or refute this concern by examining the association between β -blocker initiation and change in depressive symptoms in AMI patients.

Methods—Using data from 2 US multi-center, prospective registries of AMI patients, we examined 1-, 6-, and 12-month changes in depressive symptoms after the index hospitalization among patients who were β -blocker naïve on admission. Depressive symptoms were assessed using the validated 8-item Patient Health Questionnaire (PHQ-8), which rates depressive symptoms from 0 to 24, with higher scores indicating more depressive symptoms. A propensity-matched repeated measures linear regression model was used to compare change in depressive symptoms among patients who were and were not initiated on a β -blocker after AMI.

Results—Of 3470 AMI patients who were β -blocker naïve on admission, 3190 (91.9%) were initiated on a β -blocker and 280 (8.1%) were not. Baseline PHQ-8 scores were higher in patients not initiated on a β -blocker (mean 5.78 ± 5.45 vs. 4.88 ± 5.11 , $P=0.005$). PHQ-8 scores were progressively lower at 1, 6 and 12 months in both the β -blocker (mean decrease at 12 months, 1.16; $p<0.0001$) and no β -blocker groups (mean decrease, 1.71; $p<0.0001$). After propensity matching 201 untreated patients with 567 treated patients, initiation of β -blocker therapy was not associated with a difference in mean change in PHQ-8 scores at 1, 6 or 12 months after AMI (absolute mean difference with β -blocker initiation at 12 months of 0.08, 95% CI: -0.81 to 0.96 , $P=0.86$).

Conclusions—Initiation of β -blocker therapy after AMI was not associated with an increase in depressive symptoms. Restricting β -blocker use because of concerns about depression appears unwarranted and may lead to under-treatment of AMI patients.

Address for Correspondence: Paul S. Chan, MD, MSc, Saint Luke's Mid America Heart Institute, 4401 Wornall Road, Kansas City, MO 64111, (Phone) 816-699-3409; (Fax) 816-932-5613, pchan@saint-lukes.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

Depression; myocardial infarction; beta-blocker

Introduction

Beta-blockers (β -blockers) reduce mortality after acute myocardial infarction (AMI)¹. However, concerns about the association of β -blocker use with depression^{2,3} may contribute to its underuse after AMI^{4,5}. In fact, although β -blocker use is a performance measure for AMI patients⁶, physicians routinely cite depression as a ‘medical contraindication’ for treatment. As depression is now a recognized risk factor for poor prognosis in patients with acute coronary syndrome, as stated in a recently published American Heart Association Scientific Statement⁷, AMI patients with depression may achieve an even greater absolute risk reduction from β -blocker therapy than non-depressed patients, if treatment did not exacerbate their depressive symptoms.

Prior studies of β -blocker use and depression in AMI patients have shown mixed results. An association between treatment with β -blockers and depression in AMI patients was shown in two randomized controlled trials (RCTs)^{8,9} but not in another RCT.¹⁰ However, these RCTs did not use validated measures of depression. Subsequent studies that used standardized measures of depression found no association between β -blocker use and depression in AMI patients,¹¹⁻¹³ but these studies also had design limitations, including not adjusting for baseline depression,^{11,12} socioeconomic status, or other psychosocial factors (e.g., social support)¹¹⁻¹³ – all of which may confound the association of β -blocker use and depression. Furthermore, all prior studies in AMI patients using standardized measures of depression have included patients who were already on β -blocker treatment prior to AMI and none have assessed the association between *de novo initiation* of β -blocker therapy and depression. Finally, previous studies have not specifically assessed the effect of β -blockers on the progression of depressive symptoms in AMI patients with pre-existing symptoms of depression.

Accordingly, we sought to improve upon the limitations of prior studies by assessing the association between initiation of β -blocker treatment and subsequent change in depressive symptoms in AMI patients who were not previously treated with β -blockers, using data from 2 U.S. multi-center registries with detailed clinical, psychosocial, and socioeconomic information.

METHODS

Participants and study design

The patient population was from two similar U.S. based, multicenter, prospective AMI registries – the Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients’ Health Status (TRIUMPH) study and the Prospective Registry Evaluating Outcomes After Myocardial Infarctions: Events and Recovery (PREMIER). TRIUMPH enrolled patients from 24 hospitals between April 11, 2005 and

December 31, 2008 and patients in PREMIER were enrolled from 19 hospitals between January 1, 2003, and June 28, 2004. The type of data and the process of data collection for the 2 registries were similar and their study designs have been previously described^{14,15}.

In each study, detailed information on clinical, demographic, psychosocial and socioeconomic variables were obtained by chart abstraction and baseline interviews by trained staff within 24 to 72 hours of the index AMI admission. Patients were eligible for inclusion if they were aged 18 years or older, had elevated cardiac enzymes (troponin-I or creatinine kinase-MB) within 24 hours of hospital admission and supporting evidence suggestive of AMI, including either prolonged ischemic symptoms or electrocardiographic ST-changes. Patients were excluded if they were incarcerated, refused participation, were unable to provide consent, did not speak English or Spanish, were transferred to the participating hospital from another facility >24 hours after initial admission, or expired or were discharged prior to being contacted by the investigators. All participants provided written informed consent and the study protocol was approved by the institutional review board at each participating center.

A total of 6838 patients were enrolled into TRIUMPH and PREMIER. We excluded 240 patients who were discharged against medical advice, died in hospital, or were transferred to another hospital or to hospice. Because we were interested in examining the association between *de novo* initiation of β -blocker treatment and 1-12 month change in depressive symptoms, we excluded 2130 patients who were on β -blocker therapy prior to their index AMI and 221 patients who had a contraindication (e.g., bradycardia, heart block, hypotension) to the initiation of β -blocker therapy. We also excluded patients without either a baseline (n=217) or follow up depression assessment (n=540). Finally, as we planned to conduct a within site analysis with hierarchical models, 20 patients were excluded from 3 sites that discharged all patients on β -blockers. Our final study cohort was comprised of 3470 AMI patients from 28 hospitals.

Study Outcome: Assessment of Depressive Symptoms

The independent variable for this study was initiation of β -blocker therapy during the index AMI. The primary outcome was change in depressive symptoms up to 12 months after AMI, as measured by the Patient Health Questionnaire-8 (PHQ-8). The PHQ-8 was administered within 24 to 72 hours of admission and repeated at 1, 6 and 12 months follow up. The PHQ-8 is a validated instrument used to screen for depression¹⁶. The PHQ-8 quantifies the frequency, over the past 2 weeks, of each of 8 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)¹⁷ criteria on a 4-point Likert scale ranging from "0" (not at all) to "3" (nearly every day). Responses are summed to create a score between 0 and 24 points, with higher scores denoting more severe depressive symptoms. A PHQ-8 score of 10 is indicative of the presence of symptoms of major depression.

Other Study Variables

Sociodemographic variables collected in the cohort included age, gender, race (white, black, and other), marital and employment status, educational level (graduated vs. not graduated from college), health insurance coverage, and financial difficulties (including asking patients

whether, at the end of a month, they did “not have enough money to make ends meet”). Clinical variables included medical comorbidities (hyperlipidemia, hypertension, diabetes mellitus, peripheral arterial disease, prior AMI, prior percutaneous coronary intervention [PCI] or coronary artery bypass surgery [CABG], prior stroke, chronic kidney disease, chronic lung disease, and chronic heart failure), recent smoking, obesity (body mass index 30 kg/m^2), hematocrit, and treatment with medication or counselling for depression at the time of admission. In addition, information on AMI characteristics and severity were obtained, including type of AMI (ST elevation vs. non-ST elevation), left ventricular ejection fraction $<40\%$, presence of multi-vessel coronary artery disease on coronary angiography, and Killip class [class I/II vs. III/IV]. As initiation of β -blocker therapy may be influenced by patients' hemodynamics, we also collected information on discharge heart rate and systolic blood pressure. Lastly, we collected information on patients' perceived social support, as measured by the 7-item ENRICH Social Support Inventory (ESSI). Based on prior work, low social support was defined as a score of 3 on 2 or more items (excluding items on instrumental social support and marital status) and having a total sum score of 18¹⁸.

Statistical Analysis

Baseline differences between patients who were and were not initiated on β -blockers were compared using Student's t-test for continuous variables and Chi-square tests for categorical variables.

To determine whether there were changes in depressive symptoms over time in each group, we assessed for changes in PHQ-8 scores from baseline to 1, 6, and 12-months separately in those who were and were not discharged on β -blockers, using paired t-tests for each time point comparison. Then, to assess whether initiation of β -blocker therapy was associated with changes in depressive symptoms over time, we compared the mean change in depressive symptoms from baseline to each follow-up time point between patients initiated on β -blockers and those who were not, using a repeated measures analysis. To accomplish this, we first ensured that patients in the β -blocker and no β -blocker groups were equally matched by developing a propensity score for β -blocker treatment. A non-parsimonious propensity score was generated with a multivariable logistic regression model that included 27 baseline variables to predict initiation of β -blocker treatment. These variables included the patient sociodemographic and clinical variables described above. In addition, baseline medications or counselling for depression and baseline PHQ-8 score were included in the propensity score model. Using a caliper width no greater than 0.2 times the standard deviation of the log of the propensity score¹⁹, each patient who was not initiated on a β -blocker was then matched with up to 3 patients who were initiated on a β -blocker using variable optimal matching without replacement techniques²⁰. We confirmed that patients treated and not treated with β -blockers were well balanced by ensuring that standardized differences between the 2 groups for each covariate were $<10\%$ ²¹.

Among patients who were matched by propensity scores, we then compared whether changes in PHQ-8 scores from baseline to each follow-up time point differed between patients treated and not treated with β -blockers using repeated measures models. To further

examine whether the effect of initiation of β -Blocker therapy on depressive symptoms differed among those with symptoms of major depression (defined as a baseline PHQ-8 score ≥ 10) and those without, we included an interaction term in our model between β -blocker therapy and major depression on change in PHQ-8 scores. In addition, we conducted a sensitivity analysis to control for potential biases in loss to follow-up (i.e., patients who were excluded due to no follow-up PHQ-8 assessments). A second propensity score model was developed to predict the likelihood of follow-up assessments with the PHQ-8. The reciprocal of this probability was then used to weight the associations among responders in the repeated measures model. This model yielded similar findings (results not shown), so we have presented the primary analyses only. Finally, to incorporate assessments of depressive symptoms from all three follow-up time points, we performed a 1-way analysis of covariance (ANCOVA) analysis comparing the trajectory of depressive symptoms for the propensity-matched groups, adjusting for baseline depression as a covariate. This analysis incorporates follow-up assessments of all study patients, regardless of whether they had PHQ-8 evaluations at all or only some time points.

At least 1 study covariate was missing in 27% of patients, and more than 1 study covariate was missing in 10% of patients, with an average number of missing data fields per patient of 0.46. The covariate with the most missing data was the “number of diseased vessels” ($n=198$ [5.7%]), as coronary angiography was not performed in 197 patients, followed by final hematocrit ($n=173$ [5.0%]). Missing data were imputed using IVEWARE²⁰, and all covariates that were used in the logistic propensity model were used for imputation.

All tests for statistical significance were two-tailed and evaluated at a significance level of 0.05. All analyses were conducted with SAS 9.2 (SAS Institute, Inc, Cary, NC). Partial funding of the PREMIER registry was received from CV Therapeutics, Inc., Palo Alto, CA and the TRIUMPH registry from the National Heart, Lung and Blood Institute (P50 HL077113). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

RESULTS

Of 3470 AMI patients not previously treated with a β -blocker, 3190 (91.9%) were started on a β -blocker and 280 (8.1%) were not. Patients not initiated on β -blocker therapy were more likely to be African American, unemployed, unmarried, and to have financial difficulties (Table 1). They were also more likely to have concomitant diabetes, hypertension, congestive heart failure, pre-existing ischemic heart disease, chronic renal failure and chronic lung disease ($P<0.05$). In addition, they were less likely to have presented with an ST-elevation AMI or to have undergone coronary revascularization during the index hospitalization. Those not initiated on a β -blocker also had greater depressive symptoms at baseline (mean PHQ-8 = 5.78 vs. 4.88, $P=0.005$) and were more likely to be on antidepressant medications or receiving counseling for depression. Baseline characteristics of patients by β -blocker group, stratified by major depression (PHQ-8 score ≥ 10) are outlined in the Supplementary Appendix eTables 1 and 2.

β-Blockers and depressive symptoms

Follow-up assessments with the PHQ-8 were obtained in 2899, 2702, and 2678 patients (and therefore missing in 571 [16.5%], 768 [22.1%], and 792 [22.8%]) at the 1, 6, and 12-month follow-up, respectively. During follow-up, depressive symptoms progressively decreased on the PHQ-8 scale between admission and 1, 6 and 12 months follow up in both the β-blocker and no β-blocker groups (Table 2). On crude comparison, there was no difference between the two groups in the mean change in PHQ-8 scores from baseline to 1 month (unadjusted difference in mean change in PHQ-8 scores between the 2 groups of -0.22 , $P=0.52$), 6 months (0.08 , $P=0.83$) or 12 months (0.55 , $P=0.22$) after AMI.

The propensity score matched analysis successfully matched 201 patients not initiated on a β-blocker with 567 treated patients (model c-statistic: 0.79). After propensity score matching, we found that initiation of β-blocker therapy was not associated with a difference in mean change in PHQ-8 scores compared to the non-β-blocker group at 12 months of follow up (adjusted difference in mean change in PHQ-8 scores of 0.08 , 95% CI, -0.81 to 0.96 , $P=0.86$). Similarly, there were no differences in change in depressive symptoms at 1 and 6 month follow-up (Table 3). Additionally, an ANCOVA analysis which accounts for missing follow-up PHQ-8 assessments and incorporates data from all three time points confirmed that there was no difference in change in depressive symptoms between the 2 groups during the first 12 months of follow-up (P of 0.52).

While symptoms of major depression (PHQ-8 ≥ 10) were present at baseline in 617 of the 3470 study patients, there was no significant interaction between initiation of β-blocker therapy and baseline major depression on 1-month ($P=0.31$), 6 month ($P=0.41$) or 12 month ($P=0.10$) change in depressive symptoms. This suggests that there was no difference in change in depressive symptoms at all three follow-up time points between the β-blocker groups, regardless of whether patients had evidence of major depression on admission.

DISCUSSION

We found that *de novo* initiation of β-blocker therapy after AMI was not associated with an increase in depressive symptoms over time. Moreover, patients treated with β-blockers had a similar trajectory of 1-year change in depressive symptoms as untreated patients. Our findings thus provide important empirical evidence that β-blocker use is not associated with a higher risk of depressive symptoms after AMI and suggest that concerns about depression should not be routinely cited as a reason for not initiating β-blocker therapy in AMI patients.

Our work confirms and extends the findings of other investigators. In a meta-analysis of 15 placebo-controlled randomized trials of β-blocker therapy, no association between β-blocker use and depression was found²². However, the study populations in these trials were heterogeneous, were comprised of patients with AMI, heart failure, or hypertension and did not include patients ineligible for inclusion into the randomized trials. Furthermore, depression was self-reported as an adverse event in these clinical trials and was not systematically assessed in all patients using a standardized instrument, such as the PHQ. Two prospective observational studies using standardized diagnostic measures/interviews for depression also did not find an association between β-blocker use and depression after

AMI.^{12,13} However, the first study lacked adequate adjustment for baseline depression as assessment for depression did not occur until 8 to 10 days after AMI.¹² Although the second study did adjust for baseline depression as well as for many other potential confounding clinical factors,¹³ neither of these studies adjusted for other potential confounders of depressive symptoms, such as socioeconomic and psychosocial factors. We were able to improve upon the limitations of these prior investigations by adjusting for a number of important patient characteristics, including several key socioeconomic and psychosocial variables with the potential to confound the relationship with depression, such as education level, financial difficulties, marital status, insurance type, and social support. Furthermore, to our knowledge, our study is the first to assess whether the *initiation* of β -blocker therapy after AMI in previously untreated patients was associated with changes in depressive symptoms.

As clinicians may withhold β -blocker treatment after AMI because of concerns about depression risk, evaluating whether an association between β -blocker therapy and worsening depressive symptoms exists is important to understand, as it may have implications on AMI treatment. If no relationship exists, this caution may have the unintended consequence of under-treating AMI patients with a therapy known to reduce subsequent cardiovascular morbidity and mortality after AMI^{10,23,24}. This potential under-treatment would be further compounded in patients with a history of depression, which is well known to be independently associated with a worse AMI prognosis. In contrast to historical concerns, we found that depressive symptoms among those in whom β -blockers were initiated actually decreased over time, with PHQ-8 scores decreasing 18% at 1-month and 25% at 12-month follow up. Furthermore, we observed that depressive symptoms improved, even in patients with symptoms of major depression (PHQ-8 scores ≥ 10) at the time of their AMI. Our findings therefore suggest that initiation of β -blocker therapy after AMI was not associated with further worsening of depressive symptoms and were robust to follow-up time points of up to 1-year.

The results of our study should be considered in the context of the following limitations. Firstly, PHQ-8 is self-reported and therefore subject to response bias. Second, although we found no association between initiation of beta-blocker therapy and depressive symptoms, we did not have data to ascertain whether the reason beta-blockers were not prescribed by clinicians was due to concerns about depression. Future qualitative studies are warranted to better understand reasons for non-treatment. Third, while the propensity analysis matched patients by treatment for depression and disease severity at baseline, we did not adjust for initiation of treatment for depression or clinical events during follow up. Fourth, we did not assess serial β -blocker use over time to determine duration of treatment or medication adherence after the initial AMI. Fifth, the vast majority of patients in our study received metoprolol as their β -blocker, and it remains possible that the association between more lipophilic β -blockers, such as propranolol, and depression may be different, as was originally suggested by Waal et al²⁵. Finally, although our analysis adjusted for a wide variety of sociodemographic, clinical, and psychosocial factors, and we used a robust propensity score analysis to adjust for potential confounding, our study was observational; therefore, we cannot exclude the possibility of unmeasured confounding.

Conclusion

In a large cohort of AMI patients with, on average, mild baseline depressive symptoms, we found no evidence of an association between de novo *initiation* of β -blocker therapy and worsening depressive symptoms after 1, 6 or 12 months of follow up. Given the established morbidity and mortality benefits of β -blocker therapy after AMI, physician concerns about β -blocker use and depression may be unjustified and could lead to under-treatment of AMI patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding:

- Dr. Chan is supported by funding (K23HL102224 and 1R01HL123980) from the National Heart Lung and Blood Institute.
- The PREMIER registry received funding support from CV Therapeutics, Inc., Palo Alto, CA and CV Outcomes, Inc., Kansas City, MO.
- The TRIUMPH registry received funding support from the National Heart, Lung and Blood Institute (P50 HL077113) and CV Outcomes, Inc., Kansas City, MO.

REFERENCES

1. Freemantle N, Cleland J, Young P, Mason J, Harrison J. Beta-blockade after myocardial infarction: systematic review and meta regression analysis. *Brit Med J*. 1999; 318(7200):1730–7. [PubMed: 10381708]
2. Luijendijk HJ, Koolman X. The incentive to publish negative studies: how beta-blockers and depression got stuck in the publication cycle. *Journal of clinical epidemiology*. 2012; 65(5):488–92. [PubMed: 22342262]
3. Verbeek DE, van Riezen J, de Boer RA, van Melle JP, de Jonge P. A review on the putative association between beta-blockers and depression. *Heart Fail Clin*. 2011; 7(1):89–99. [PubMed: 21109212]
4. Sinha S, Goldstein M, Penrod J, et al. Beta-blocker use among veterans with systolic heart failure. *J Gen Intern Med*. 2006; 21(12):1306–9. [PubMed: 17105526]
5. Everly MJ, Heaton PC, Cluxton RJ Jr. Beta-blocker underuse in secondary prevention of myocardial infarction. *The Annals of pharmacotherapy*. 2004; 38(2):286–93. [PubMed: 14742768]
6. Drozda J Jr, Messer JV, Spertus J, et al. ACCF/AHA/AMA-PCPI 2011 performance measures for adults with coronary artery disease and hypertension: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures and the American Medical Association-Physician Consortium for Performance Improvement. *Circulation*. 2011; 124(2):248–70. [PubMed: 21670226]
7. Lichtman JH, Froelicher ES, Blumenthal JA, et al. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations: a scientific statement from the American Heart Association. *Circulation*. 2014; 129(12):1350–69. [PubMed: 24566200]
8. Hansteen V, Moinichen E, Lorentsen E, et al. One year's treatment with propranolol after myocardial infarction: preliminary report of Norwegian multicentre trial. *Br Med J (Clin Res Ed)*. 1982; 284(6310):155–60.
9. Julian DG, Prescott RJ, Jackson FS, Szekely P. Controlled trial of sotalol for one year after myocardial infarction. *Lancet*. 1982; 1(8282):1142–7. [PubMed: 6122937]

10. Beta-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction: I. mortality results. *JAMA*. 1982; 247(12):1707–14. [PubMed: 7038157]
11. Crane PB, Oles KS, Kennedy-Malone L. Beta-blocker medication usage in older women after myocardial infarction. *Journal of the American Academy of Nurse Practitioners*. 2006; 18(10): 463–70. [PubMed: 16999711]
12. Schleifer SJ, Slater WR, Macari-Hinson MM, et al. Digitalis and beta-blocking agents: effects on depression following myocardial infarction. *American heart journal*. 1991; 121(5):1397–402. [PubMed: 1673283]
13. van Melle JP, Verbeek DE, van den Berg MP, Ormel J, van der Linde MR, de Jonge P. Beta-blockers and depression after myocardial infarction: a multicenter prospective study. *Journal of the American College of Cardiology*. 2006; 48(11):2209–14. [PubMed: 17161247]
14. Spertus JA, Peterson E, Rumsfeld JS, Jones PG, Decker C, Krumholz H. The prospective registry evaluating myocardial infarction: Events and recovery (PREMIER)—Evaluating the impact of myocardial infarction on patient outcomes. *American heart journal*. 2006; 151(3):589–97. [PubMed: 16504619]
15. Arnold SV, Chan PS, Jones PG, et al. Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients' Health Status (TRIUMPH): Design and Rationale of a Prospective Multicenter Registry. *Circulation: Cardiovascular Quality and Outcomes*. 2011; 4(4): 467–76. [PubMed: 21772003]
16. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001; 16(9):606–13. [PubMed: 11556941]
17. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fourth Edition.. American Psychiatric Association; Washington DC: 1994.
18. The ENRICHD Investigators. Enhancing recovery in coronary heart disease patients (ENRICHD): study design and methods. *The ENRICHD investigators*. *American heart journal*. 2000; 139(1 Pt 1):1–9. [PubMed: 10618555]
19. Rosenbaum PR, Rubin DB. Constructing a Control Group Using Multivariate Matched Sampling Methods That Incorporate the Propensity Score. *The American Statistician*. 1985; 39(1):33–8.
20. Raghunathan, T.; Solenberger, P.; Van Hoewyk, J. *IVeWare: Imputation and Variance Estimation Software - User Guide*. Survey Research Center, Institute for Social Research University of Michigan; Michigan: 2002.
21. Normand ST, Landrum MB, Guadagnoli E, et al. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. *Journal of clinical epidemiology*. 2001; 54(4):387–98. [PubMed: 11297888]
22. Ko DT, Hebert PR, Coffey CS, Sedrakyan A, Curtis JP, Krumholz HM. Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *JAMA*. 2002; 288(3):351–7. [PubMed: 12117400]
23. Hjalmarson Å, Herlitz J, Málek I, et al. Effect on mortality of metoprolol in acute myocardial infarction: A Double-blind Randomised Trial. *Lancet*. 1981; 318(8251):823–7. [PubMed: 6116950]
24. The Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *NEnglJMed*. 1981; 304:801–7.
25. Waal HJ. Propranolol-induced depression. *Br Med J*. 1967; 2(5543):50. [PubMed: 6021004]

Table 1**Patient Characteristics**

	β-blocker (n=3190)	No β-blocker (n= 280)	P Value
Sociodemographic factors			
Age, years (mean ± SD)	57.8±12.0	59.3 ± 12.3	0.06
Male sex (%)	69.6	64.3	0.07
African American (%)	18.9	33.7	<0.001
Employed (%)	57.2	41.0	<0.001
Graduated from College (%)	22.9	18.2	0.07
Married (%)	60.0	53.6	0.038
Insured (%)	81.8	81.0	0.74
Financial difficulties (%)	16.6	23.8	0.002
Medical History (%)			
Hyperlipidemia	42.0	42.1	0.96
Diabetes mellitus	21.6	31.4	<0.001
Hypertension	52.9	60.0	0.02
Current Smoking	41.9	36.9	0.10
Congestive heart failure	4.0	11.8	<0.001
Peripheral vascular disease	4.1	5.4	0.33
Cerebrovascular disease	4.9	5.4	0.71
Previous myocardial infarction	10.0	19.6	<0.001
Previous PCI	9.7	15.4	0.003
Previous CABG	4.5	11.4	<0.001
Chronic renal failure	3.7	6.8	0.01
Chronic lung disease	7.0	18.2	<0.001
Current medication or counseling for depression	10.5	15.4	0.01
Clinical Characteristics			
Body Mass Index (mean ± SD)	29.3 ± 6.2	29.4 ± 6.9	0.90
Killip class III or IV (%)	2.1	2.8	0.45
Systolic blood pressure < 100 at discharge (%)	14.0	11.7	0.32
Heart rate < 60 at discharge (%)	11.9	12.8	0.68
LVEF < 40% (%)	18.1	20.4	0.35
STEMI (%)	54.0	26.1	<0.001
Revascularization during admission	82.5	53.2	<0.001
Multi-vessel coronary disease (%)	42.1	42.4	0.94
Enriched Social Support Score (mean ± SD)	22.1 ± 4.3	21.9 ± 4.7	0.33

Abbreviations: PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; LVEF: Left ventricular ejection fraction; STEMI: ST elevation myocardial infarction

Table 2

Change in Depressive Symptoms Within Each β -blocker Group at 1, 6 & 12 Months After Acute Myocardial Infarction.*

	β -blocker	No β -blocker
Patients with baseline and 1-month PHQ-8	N = 2674	N = 225
Baseline, mean (SD)	4.83 (5.11)	5.44 (5.45)
1 month, mean (SD)	3.97 (4.52)	4.80 (4.90)
Mean difference in PHQ-8 (95% CI)	-0.86 (-1.05, -0.67)	-0.64 (-1.28, 0.004)
P value for mean difference	P = <0.0001	P = 0.05
Patients with baseline and 6-month PHQ-8	N = 2488	N = 214
Baseline, mean (SD)	4.79 (5.01)	6.03 (5.50)
6 months, mean (SD)	3.64 (4.67)	4.80 (5.25)
Mean difference in PHQ-8 (95% CI)	-1.15 (-1.34 to -0.95)	-1.23 (1.99 to -0.48)
P value for mean difference	P = <0.0001	P = 0.0015
Patients with baseline and 12-month PHQ-8	N = 2480	N = 198
Baseline, mean (SD)	4.61 (4.94)	5.72 (5.72)
12 months, mean (SD)	3.45 (4.57)	4.01 (5.07)
Mean difference in PHQ-8 (95% CI)	-1.16 (-1.36 to -0.96)	-1.71 (-2.55 to -0.86)
P value for mean difference	P = <0.0001	P = <0.0001

For each of the evaluations of change in depressive symptoms from baseline to follow-up, we report the PHQ-8 scores at each time point, the mean difference between baseline and the follow-up time point, and the P value for a significant change *within* each β -blocker group.

* The composition of the cohorts varies for each time period assessed due to variation in follow up hence the different mean baseline values.

Table 3

Difference in mean change in PHQ-8 scores Between the β -blocker and non- β -blocker groups.*

Comparison Period	Adjusted difference in mean change in PHQ-8 scores (95% CI)	P Value
Baseline to 1 month	-0.22 (-1.02, 0.58)	0.58
Baseline to 6 months	-0.37 (-1.19, 0.45)	0.38
Baseline to 12 months	0.08 (-0.81, 0.96)	0.86

Using a matched propensity score analysis, the change in depressive symptoms in patients treated and not treated with β -blockers between baseline and each follow-up time point were compared and found to be similar.

* Propensity (adjusted) score analysis matched 201 patients not initiated on a β -blocker with 567 patients initiated on a β -blocker. A negative value suggests greater decreases in depressive symptoms among those treated with β -blockers, while a positive value suggests smaller decreases.