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Atenolol Is Associated with Lower Day of Surgery Heart Rate as compared to Long and Short-acting Metoprolol

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Abstract

Objectives—We analyzed the association between outpatient beta-blocker type and day-of-surgery heart rate in ambulatory surgical patients. We further investigated whether differences in day of surgery heart rate between atenolol and metoprolol could be explained by once-daily versus twice-daily dosing regimens.

Design—Retrospective observational study.

Setting—VA Hospital

Participants—Ambulatory surgical patients on chronic atenolol or metoprolol.

Interventions—None.

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Meeting Presentations: A preliminary analysis of these data appeared in an abstract poster that was presented at the American Society of Anesthesiologists; October 19, 2011; Chicago, IL.

Measurements and Main Results—Using a propensity-score matched cohort, we compared day of surgery heart rates of patients prescribed atenolol versus metoprolol. We then differentiated between once-daily and twice-daily metoprolol formulations and compared day of surgery heart rates within a general linear model. Day of surgery heart rates in patients prescribed atenolol vs. any metoprolol formulation were slower by a mean of 5.1 beats/min (66.6 vs. 71.7; 95% CI of difference 1.9 to 8.3, $p=0.002$), a difference that was not observed in preoperative primary care visits. The general linear model demonstrated that patients prescribed atenolol (typically QD dosing) had a mean day of surgery heart rate 5.6 beats/min lower compared to patients prescribed once-daily metoprolol succinate (68.9 vs. 74.5; 95% CI of difference: -8.6 to -2.6 , $p<0.001$) and 3.8 beats/minute lower compared to patients prescribed twice-daily metoprolol tartrate (68.9 vs. 72.7; 95% CI of difference: -6.1 to -1.6 , $p<0.001$). Day of surgery heart rates were similar between different formulations of metoprolol (95% CI of difference: -1.0 to $+4.6$, $p=0.22$).

Conclusions—Atenolol is associated with lower day of surgery heart rate vs. metoprolol. The heart rate difference is specific to the day of surgery and is not explained by once-daily versus twice-daily dosing regimens.

Keywords

Perioperative Beta Blockade; Atenolol; Metoprolol

Background

Recent data on chronic use of perioperative beta blockade have suggested a beneficial effect of atenolol as compared to metoprolol on post-operative mortality, but the basis for this association remains unknown.^{1, 2} Other studies have demonstrated a positive association between preoperative heart rate and cardiac ischemia,³ and it has been suggested that a lowering of heart rate may be the primary means by which beta blockers exert cardioprotective effects.^{3, 4} If patients prescribed atenolol versus metoprolol demonstrate a lower day-of-surgery (DOS) heart rate, such a difference could therefore help to explain some of the observed mortality benefit.

In a meta-analysis of randomized clinical trials of perioperative beta blockade, metoprolol was found to have less effect on heart rate compared to other beta blockers,⁴ but direct comparisons within a single cohort examining DOS heart rate among patients prescribed outpatient atenolol versus metoprolol are lacking in the medical literature. The present study used a propensity score-matched cohort of ambulatory surgical patients prescribed either oral atenolol or metoprolol to test the hypothesis that atenolol is associated with different DOS heart rate as compared to metoprolol.

Previous work on this subject has also suggested that the observed perioperative benefit of atenolol as compared to metoprolol may be due to a higher incidence of beta blocker withdrawal among patients prescribed metoprolol.¹ This argument has been based on the suggestion that users of a short-acting, twice-daily beta blocker such as metoprolol tartrate may be more prone to presurgical non-compliance than users of a typically once-daily beta blocker such as atenolol.¹ Although such a suggestion may appeal to conventional wisdom, the literature on preoperative beta blocker compliance remains preliminary,⁵ and conclusions regarding differing patterns of compliance between once-daily atenolol and twice-daily metoprolol remain speculative. With the popularization of extended release metoprolol formulations (i.e. metoprolol succinate), it is now possible to test this hypothesis by stratifying metoprolol-users into two groups based on once-daily versus twice-daily formulations. Accordingly, in the present study, we conducted a second analysis using a general linear model to perform a pairwise comparison of mean adjusted DOS heart rate among patients prescribed outpatient oral formulations of atenolol, metoprolol tartrate

(BID), and metoprolol succinate (QD). For this second analysis our hypothesis was that if perioperative compliance effects related to dosing schedules led to differences in DOS heart rate, then heart rates would differ between atenolol and metoprolol tartrate (short-acting, twice-daily dosing) but not between atenolol and metoprolol succinate (long-acting, once daily dosing).

Materials and Methods

Database queries

After IRB approval including a waiver of the requirement of informed consent, we created the Veterans Administration Perioperative Outcomes Research (VAPOR) database as described previously.⁶ Briefly, queries of the Veterans Health Information Systems and Technology Architecture (VISTA) database at our local VA hospital from June 2006–December 2009 identified patients who presented from home for surgery at the study institution. For the present study, the VAPOR cohort was limited to patients who filled a prescription at the VA pharmacy for oral atenolol or metoprolol within 3 months prior to surgery and who had vital signs recorded at the primary care center of the same institution within 183 days (six months) prior to surgery.

Preoperative primary care vital signs, initial day of surgery vital signs, demographic data, surgery type, anti-hypertensive medications, and medical comorbidity data were included in the dataset. Demographics included age, gender, height, and weight. Surgery type was dichotomized into cardiothoracic or vascular and all others. Medical comorbidities were determined by a query of each patient's International Classification of Disease - 9 clinical modification (ICD-9 CM) diagnostic codes up to and including the date of surgery. Using the Veterans Aging Cohort Study (VACS)^{7–9} diagnostic groupings, a history of each of the following comorbidities was included in our analyses: atrial fibrillation, cerebrovascular disease (including stroke and transient ischemic attack), congestive heart failure, coronary artery disease, diabetes, hypertension, kidney disease, peripheral vascular disease, psychiatric disorder (including any VACS-delineated mood or thought disorder), and substance abuse (including alcohol or drug abuse).

Pharmacy data on the following outpatient anti-hypertensive medications other than beta blockers were included in the analysis: ACE-inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers, antianginals (i.e. nitrates), and thiazide-type diuretics. In addition, we included in the analysis the number of days preoperatively since the most recent beta blocker refill occurred.

Prior to analysis, data were checked for outliers in heart rate, height, and weight which triggered review of the individual medical record and exclusion of any data that were felt likely by author consensus to be clerical errors. Although the method of vital sign recording was not dictated within this retrospective observational study, the general practice among the preoperative and primary care clinics at the study institution is to record heart rates via digital readout from an automated pulse oximeter and blood pressures via automated oscillometric cuff measurement. These numbers are then entered into the electronic health record by the recording clinician.

After formation of the final cohort, we then performed two analyses. The first involved the formation of a propensity score-matched cohort of patients prescribed atenolol and metoprolol. Matched pairs were then analyzed by means of a paired T-test to detect a difference in the presenting DOS heart rate between patients prescribed atenolol and metoprolol. The second analysis used the method of least squares within a general linear

model to conduct a pairwise comparison of mean adjusted DOS heart rate between patients prescribed atenolol, metoprolol succinate, and metoprolol tartrate.

Statistical Analyses

Statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc. Cary, NC). Descriptive analyses of variables are presented as mean (SD) or number (percentage) as appropriate. Two-tailed results of all hypothesis tests are reported, and a p -value of less than 0.05 was considered to be statistically significant.

Propensity Score Matching Protocol

Propensity scores estimating the probability of filling an outpatient prescription for atenolol versus metoprolol were calculated using a non-parsimonious logistic regression model in which outpatient beta blocker type (atenolol or metoprolol) was the dichotomous dependent variable. The following covariates were included: age, gender, primary care heart rate, primary care systolic and diastolic blood pressure, height, weight, body surface area (determined according to the Mosteller formula),¹⁰ surgery type (dichotomized as cardiothoracic or vascular surgery and all others), VACS comorbidity groupings for a preoperative history of coronary artery disease, hypertension, diabetes, atrial fibrillation, peripheral vascular disease, kidney disease, cerebrovascular disease, psychiatric disorder, and substance abuse. Preoperative prescriptions for ACE-inhibitors or ARBs (combined into a single variable), calcium channel blockers, antianginals, and thiazide-type diuretics were also included as dichotomous variables. If patients were taking a combination medicine containing active ingredients from two different antihypertensive classes, patients were considered to be on both classes of drug.

Patients prescribed atenolol were individually matched with patients prescribed metoprolol in a 1:1 fashion based on the similarity of propensity scores. Matching proceeded via a 5 to 1 greedy matching algorithm in which patients prescribed atenolol were matched to patients prescribed metoprolol first based on five digits of the propensity score. For patients not able to match on all five digits, an attempt was made to match on four digits of the propensity score. This algorithm continued down to 1-digit matching of the propensity score with the remainder of patients who remained unmatched excluded from the propensity score-matched analysis.¹¹

After this matching procedure, the balance of the covariates between the two groups was assessed using a paired t -test for continuous measures and McNemar's test for categorical measures. DOS systolic and diastolic blood pressures were also compared by means of a paired t -test between matched pairs of subjects in order to determine whether a significant difference was present in these variables that would necessitate controlling for these variables in the analysis of the outcome DOS heart rate. After similarity between the matched pairs was demonstrated for all of these potential confounders, the null-hypothesis that DOS presenting heart rate was the same in patients prescribed atenolol versus metoprolol was assessed by means of a paired t -test.

General linear model protocol

For the second part of our analysis, we distinguished between patients prescribed atenolol, metoprolol succinate (QD), and metoprolol tartrate (BID) and then modeled the effect of the three beta blockers on mean initial DOS heart rate using the method of least squares within a general linear model. For the model, we considered for inclusion as covariates the same variables that were used in the logistic regression for creation of the propensity score as well as the DOS systolic and diastolic blood pressures. Multi-collinearity was assessed by examining the tolerance diagnostic factor, with a value of 0.1 or less regarded as indicative

of multicollinearity. Following the assessment of collinearity, least squares means of DOS heart rate for the three types of beta blocker were calculated within the general linear model and compared in a pairwise fashion.

Results

The initially constructed dataset was comprised of 516 Veterans. A check for outliers identified two patients with aberrant heart rate or height and weight, leaving 514 patients retained for the analyses. Of these, 184 (35.8%) patients were prescribed atenolol and 330 (64.2%) were prescribed metoprolol. A flow diagram summarizing the formation of the cohort out of the VAPOR database is shown in Figure 1.

For the 514 patients subject to analysis, the mean age was 68.7 years (SD=10.9), 15 (2.9%) were female, and 94 (18.3%) were scheduled for cardiothoracic or vascular surgery. Descriptive characteristics for all of the included variables stratified by beta blocker type both before and after matching on the propensity score are listed in table 1. Similar to prior studies,² in unadjusted analysis patients prescribed metoprolol had a higher prevalence of coronary artery disease, congestive heart failure, and atrial fibrillation than patients prescribed atenolol. They were also more likely to present for cardiothoracic or vascular surgery and less likely to have a diagnosis of hypertension or to be prescribed a thiazide diuretic. Again in unadjusted analysis, patients prescribed metoprolol did not differ from those prescribed atenolol on preoperative primary care heart rate (74.3 vs. 72.5, $p=0.19$) but demonstrated a significantly higher DOS heart rate (71.7 vs. 66.9, $p<0.001$).

Propensity Score Matching Results

Table 1 lists the results of the propensity score matching procedure for each variable. A total of 294 of 514 patients were matched with our algorithm. The matched samples demonstrated trivial differences between matched pairs on all confounders considered (p -value for difference >0.2) for all baseline variables (see table 1). In the matched sample, heart rates in the atenolol group as compared to the metoprolol group were slower by a mean of 5.1 beats/min (66.6 vs. 71.7; 95% CI of difference 1.9 to 8.3, $p=0.002$). As expected in this small sample of ambulatory patients, there was no significant difference in death within 30 days between the matched groups (one patient in each group died).

General Linear Model Results

Of the 330 patients prescribed metoprolol, 87 (26%) were prescribed metoprolol succinate (QD) and 243 (74%) were prescribed metoprolol tartrate (BID). Univariate analyses of all covariates stratified by the three beta blockers are listed in table 2. Because there was a high degree of collinearity between body surface area and height and weight, body surface area was dropped from the multivariable analysis. The final general linear model included the DOS heart rate as the dependent variable, with adjustment for all other covariates from table 2. We found that patients prescribed atenolol had a mean DOS heart rate that was 5.6 beats/min lower compared to patients prescribed once daily metoprolol succinate (68.9 vs. 74.5; 95% CI of difference: -8.6 to -2.6 , $p<0.001$, Figure 2) and 3.8 beats/minute lower compared to patients prescribed twice-daily metoprolol tartrate (68.9 vs. 72.7; 95% CI of difference: -6.1 to -1.6 , $p<0.001$, Figure 2). DOS heart rates were similar between the two groups prescribed different formulations of metoprolol (95% CI of difference: -1.0 to $+4.6$, $p=0.22$, Figure 2).

Discussion

Motivated by prior observations reporting a beneficial effect of atenolol as compared to metoprolol on postoperative outcomes, the present analysis investigated whether such differences could be explained in part by differences in DOS heart rate between the two beta blockers. Analyses of beta blocker effects in observational studies are complicated by the finding that patients taking metoprolol have a higher prevalence of several comorbid diseases than those taking atenolol.² In addition to controlling for such comorbidities, the present study sought to minimize the influence of unmeasured confounding on DOS heart rate by including a recent preoperative primary care heart rate in our models. We theorized that many sources of potential unmeasured bias would likely have similar effects on heart rate during a recent primary care visit as on the initial DOS measurement.

Having attempted to control for the underlying differences between populations receiving these two beta blockers, our data do indeed demonstrate lower DOS heart rate in patients presenting from home for surgery prescribed outpatient atenolol versus metoprolol. The effect is present regardless of whether patients are prescribed long or short-acting metoprolol formulations and persists after controlling for several demographic and comorbid characteristics, including baseline primary care heart rate. It is possible that the reduced perioperative mortality previously reported in association with atenolol versus metoprolol can be explained in part by differential effects on DOS heart rate. We hasten to add that though the heart rate differences in the present study were highly statistically significant, the question of their clinical significance remains a point of speculation. Feringa, *et al.* found that preoperative heart rate was independently associated with post operative cardiovascular morbidity in high risk surgery patients and thus offers some support in this regard.³ Nevertheless, conclusions regarding a causal connection between the observed heart rate differences in our study and the putative mortality benefit of atenolol over metoprolol remain to be established in the context of appropriately designed prospective clinical trials.

A second motivation for our study was to explore the suggestion by previous investigations¹ that differences in the clinical effects of atenolol and metoprolol may stem from compliance differences between once-daily and twice-daily dosage schedules. In this regard, we find it particularly interesting that the observed heart rate benefit associated with atenolol in this study was apparent versus both once a day and twice a day formulations of metoprolol. Our finding is consistent with prior studies of medication adherence that have demonstrated no significant compliance difference between once-daily and twice-daily dosing regimens.¹² If major compliance-related effects on heart rate exist in our data, they are likely a consequence of factors other than dosage schedules. Factors such as cost or side-effect profiles may also underlie compliance differences. Perioperative beta blocker compliance behaviors on the part of patients have received limited attention,⁵ and definitive conclusions regarding patterns of perioperative beta blocker compliance await additional prospective studies specifically focused on the issue. Our data however, do not support the previous suggestion made in the medical literature¹ that observed heart rate differences between users of atenolol and metoprolol are due to once daily vs. twice daily dosing schedules.

Rather than compliance effects, our data may reflect more fundamental differences in the pharmacokinetics of atenolol versus metoprolol. Such differences have recently been summarized by Wallace, *et al.* in the context of their work looking at perioperative beta-blockade in another sample of United States Veterans.² As referenced by these investigators, variations in metoprolol metabolism among different cytochrome CYP2D6 phenotypes have been described. Metabolic differences may lead to more pronounced variation in the degree of heart rate regulation when otherwise equipotent doses of atenolol and metoprolol are

administered to a population.¹³ A definitive explanation of the mechanisms underlying the observed heart rate differences has yet to be determined and awaits further study.

The pattern of heart rate differences in our study is consistent with a similar finding from a crossover study conducted outside the perioperative period in which post-myocardial infarction patients prescribed atenolol had a lower heart rate in response to exercise than those prescribed metoprolol.¹⁴ In that context, heart rate differences between atenolol and metoprolol were not seen at baseline but emerged in the context of an external stressor. In this study, we similarly observed that differences in heart rate were not seen in primary care but emerged on the DOS. We speculate that the anticipatory stress of the immediate preoperative environment may elicit differences in beta blocker effects that only become apparent in some individuals under conditions of increased sympathetic tone. The theory underlying such speculation may find some support in previous studies demonstrating that acute cardiac responses to mental stressors differ among individuals. Moreover, such differences in stress response have been found to predict future arrhythmias.^{15–17} If atenolol is demonstrated to be superior to metoprolol at blunting the anticipatory stress response of the DOS, this may help to partially explain the lower DOS heart rate and the possible reduced mortality among patients prescribed atenolol versus metoprolol.

Limitations

A major limitation of this study is the reliance on preoperative heart rate measurements without similar data from the intraoperative or postoperative period. Because the study institution has not yet transitioned to a perioperative electronic record keeper, vital signs data from the operating room and recovery area do not populate the VISTA database upon which the current analyses rely. As part of a future investigation, it would be interesting to measure the extent to which heart rate differences between atenolol and metoprolol persist in response to stressors in the operating room and in the hours following surgery.

Another potential limitation of this study involves its observational nature. In addition to the question of their clinical significance, our heart rate findings themselves may be biased by unrecognized confounding effects and await confirmation in the context of prospective randomized trials. Our reliance on administrative markers for comorbid diagnoses also may have introduced bias into the analyses, especially given the baseline differences in disease prevalence that are known to exist between the atenolol and metoprolol populations. We attempted to address many potential sources of confounding by including a recent baseline heart rate in our analyses. By comparing groups with similar primary care heart rates, our data imply that the observed DOS heart rate differences were not confounded by unmeasured baseline differences between groups. We also limited the analyses to patients arriving from home in order to exclude patients with acute heart rate changes associated with a preoperative hospitalization. Nevertheless, as with any observational study of this kind, the risk of unrecognized confounding still persists. Our study should therefore be viewed as an indication of the importance of future research focusing on differential effects of beta blockers in the perioperative period.

Conclusion

In conclusion, among patients prescribed oral beta blockers presenting from home for surgery, atenolol is associated with significantly lower initial DOS heart rate as compared with metoprolol. The difference is not present in recent primary care measurements in the same population, and it persists in relationship to both long and short-acting metoprolol. Heart rate differences between atenolol and metoprolol in our population were therefore specific to the day of surgery and unlikely to be explained by compliance effects from different dosing schedules.

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References

1. Redelmeier D, Scales D, Kopp A. Beta blockers for elective surgery in elderly patients: population based, retrospective cohort study. *BMJ*. 2005; 331(7522):932. [PubMed: 16210252]
2. Wallace AW, Au S, Cason BA. Perioperative β -blockade: atenolol is associated with reduced mortality when compared to metoprolol. *Anesthesiology*. 2011; 114(4):824–836. [PubMed: 21372680]
3. Feringa HHH, Bax JJ, Boersma E, Kertai MD, Meij SH, Galal W, Schouten O, Thomson IR, Klooktwijk P, van Sambeek MRHM, Klein J, Poldermans D. High-dose beta-blockers and tight heart rate control reduce myocardial ischemia and troponin T release in vascular surgery patients. *Circulation*. 2006; 114(1 Suppl):I344–I349. [PubMed: 16820598]
4. Beattie WS, Wijesundera DN, Karkouti K, McCluskey S, Tait G. Does tight heart rate control improve beta-blocker efficacy? An updated analysis of the noncardiac surgical randomized trials. *Anesthesia & Analgesia*. 2008; 106(4):1039–1048. [PubMed: 18349171]
5. Schonberger RB, Feinleib J, Lukens CL, Turkoglu OD, Haspel K, Burg M. Beta-blocker withdrawal among patients presenting for surgery from home. *Journal of Cardiothoracic & Vascular Anesthesia*. 2012
6. Schonberger RB, Burg MM, Holt NF, Lukens CL, Dai F, Brandt C. The relationship between day-of-surgery and primary care blood pressure among Veterans presenting from home for surgery. Is there evidence for anesthesiologist-initiated blood pressure referral? *Anesthesia & Analgesia*. 2012; 114(1):205–214. [PubMed: 22075017]
7. Goulet JL, Fultz SL, McGinnis KA, Justice AC. Relative prevalence of comorbidities and treatment contraindications in HIV-mono-infected and HIV/HCV-co-infected veterans. *AIDS*. 2005; 19(Suppl 3):S99–S105. [PubMed: 16251836]
8. Goulet JL, Fultz SL, Rimland D, Butt A, Gibert C, Rodriguez-Barradas M, Bryant K, Justice AC. Aging and infectious diseases: do patterns of comorbidity vary by HIV status, age, HIV severity? *Clinical Infectious Diseases*. 2007; 45(12):1593–1601. [PubMed: 18190322]
9. Justice AC, Lasky E, McGinnis KA, Skanderson M, Conigliaro J, Fultz SL, Crothers K, Rabeneck L, Rodriguez-Barradas M, Weissman SB, Bryant K, Team VP. Medical disease and alcohol use among veterans with human immunodeficiency infection: A comparison of disease measurement strategies. *Medical Care*. 2006; 44(8 Suppl 2):S52–S60. [PubMed: 16849969]
10. Mosteller RD. Simplified calculation of body-surface area. *New England Journal of Medicine*. 1987; 317(17):1098. [PubMed: 3657876]
11. Parsons, L. Proceedings of the Twenty-Sixth Annual SAS® Users Group International Conference; 2001. Cary, NC: SAS Institute Inc.; 2001. Reducing bias in a propensity score matched-pair sample using greedy matching techniques; p. 214–226.
12. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clinical Therapeutics*. 2001; 23(8):1296–1310. [PubMed: 11558866]
13. Freestone S, Silas J, Lennard M, Ramsay L. Comparison of two long-acting preparations of metoprolol with conventional metoprolol and atenolol in healthy men during chronic dosing. *British Journal of Clinical Pharmacology*. 1982; 14:713–718. [PubMed: 7138751]
14. Kardos A, Long V, Bryant J, Singh J, Sleight P, Casadei B. Lipophilic versus hydrophilic β_1 blockers and the cardiac sympatho-vagal balance during stress and daily activity in patients after acute myocardial infarction. *Heart*. 1998; 79:153–160. [PubMed: 9538308]
15. Burg MM, Graeber B, Vashist A, Collins D, Earley C, Liu J, Lampert R, Soufer R. Noninvasive detection of risk for emotion-provoked myocardial ischemia. *Psychosomatic Medicine*. 2009; 71(1):14–20. [PubMed: 18941131]

16. Lampert R, Joska T, Burg MM, Batsford WP, McPherson CA, Jain D. Emotional and physical precipitants of ventricular arrhythmia. *Circulation*. 2002; 106(14):1800–1805. [PubMed: 12356633]
17. Lampert R, Shusterman V, Burg M, McPherson C, Batsford W, Goldberg A, Soufer R. Anger-induced T-wave alternans predicts future ventricular arrhythmias in patients with implantable cardioverter-defibrillators. *Journal of the American College of Cardiology*. 2009; 53(9):774–778. [PubMed: 19245968]

Figure 1.
Flow diagram of patient selection and analysis.

Figure 2.

Least squares mean day of surgery heart rate for patients prescribed each of the three outpatient beta blockers. Error bars represent the standard error of the least squares means. P-values are calculated for the three pairwise comparisons as indicated.

Table 1
Descriptive Characteristics of The Cohort Before and After Propensity Score Matching

Variables	Unmatched cohort			Cohort after propensity score matching		
	Atenolol (N=184) Mean (sd) or Number (%)	Metoprolol (N=330) Mean (SD) or Number (%)	P for difference	Atenolol (N=147) Mean (SD) or Number (%)	Metoprolol (N=147) Mean (SD) or Number (%)	P for difference
Demographics:						
Age (years)	68.0 (11.6)	69.0 (10.4)	0.33	68.7 (11.7)	67.8 (10.2)	0.47
Male gender	176 (95.7%)	323 (97.9%)	0.18	144 (98.0%)	143 (97.3%)	0.71
Height (cm)	174.2 (7.9)	173.8 (8.1)	0.60	174.0 (7.0)	173.7 (8.8)	0.77
Weight (kg)	94.4 (24.2)	90.0 (18.8)	0.04	91.8 (20.9)	90.9 (20.8)	0.71
Body Surface Area	2.12 (0.29)	2.08 (0.24)	0.06	2.1 (0.26)	2.1 (0.25)	0.70
Days since last Beta Blocker Refill	40.9 (25.0)	40.6 (25.1)	0.88	39.9 (24.1)	39.9 (24.8)	0.99
Cardiothoracic/Vascular Surgery	20 (10.9%)	74 (22.4%)	0.001	20 (13.6%)	17 (11.6%)	0.58
Comorbid Condition:						
Coronary Artery Disease	85 (46.2%)	216 (65.5%)	<0.001	77 (52.4%)	75 (51.0%)	0.79
Congestive Heart Failure	21 (11.4%)	69 (20.9%)	0.008	20 (13.6%)	21 (14.3%)	0.86
Atrial Fibrillation	24 (13%)	75 (22.7%)	0.007	24 (16.3%)	24 (16.3%)	1.0
Hypertension	177 (96.2%)	302 (91.5%)	0.05	140 (95.2%)	140 (95.2%)	1.0
Diabetes Mellitus	78 (42.4%)	145 (43.9%)	0.78	63 (42.9%)	70 (47.6%)	0.39
Peripheral Vascular Disease	61 (33.2%)	127 (38.5%)	0.3	53 (36.1%)	51 (34.7%)	0.79
Kidney Disease	14 (7.6%)	41 (12.4%)	0.10	13 (8.8%)	10 (6.8%)	0.51
Psychiatric Disorder	84 (45.7%)	122 (37.0%)	0.06	60 (40.8%)	60 (40.8%)	1.0
Substance Abuse	44 (23.9%)	73 (22.1%)	0.66	35 (23.8%)	36 (24.5%)	0.89
Cerebrovascular Disease	36 (19.6%)	73 (22.1%)	0.57	29 (19.7%)	30 (20.4%)	0.89
Anti-hypertensive Medication:						
Antianginal	13 (7.1%)	47 (14.2%)	0.01	13 (8.8%)	9 (6.1%)	0.39
ACE-Inhibitor or ARB	62 (33.7%)	111 (33.6%)	1.0	53 (36.1%)	51 (34.7%)	0.81
Calcium Channel Blocker	43 (23.4%)	55 (16.7%)	0.08	34 (23.1%)	26 (17.7%)	0.22
Thiazide Diuretic	45 (24.5%)	47 (14.2%)	0.01	28 (19.1%)	28 (19.1%)	1.0

Variables	Unmatched cohort			Cohort after propensity score matching		
	Atenolol (N=184) Mean (sd) or Number (%)	Metoprolol (N=330) Mean (SD) or Number (%)	P for difference	Atenolol (N=147) Mean (SD) or Number (%)	Metoprolol (N=147) Mean (SD) or Number (%)	P for difference
Presenting Vital Signs:						
Primary Care SBP (mmHg)	132.3 (16.5)	131.9 (17.8)	0.82	132.6 (17.1)	133.3 (18.1)	0.74
Primary Care DBP (mmHg)	74.0 (12.7)	73.4 (12.4)	0.58	73.8 (12.9)	73.4 (12.6)	0.78
Primary Care Heart Rate (beats/min)	72.5 (14.9)	74.3 (15.0)	0.18	73.3 (15.8)	73.5 (15.2)	0.93
DOS SBP (mmHg)	136.4 (19.9)	137.2 (20.6)	0.66	136.5 (20.8)	137.7 (21.0)	0.62
DOS DBP (mmHg)	74.4 (10.8)	75.3 (10.9)	0.36	74.2 (11.0)	75.7 (10.5)	0.21
DOS Heart Rate (beats/min)	66.9 (12.1)	71.7 (13.8)	<0.001	66.6 (12.2)	71.7 (15.2)	0.002

Table 2
Unadjusted Population Characteristics Stratified Into Three Beta Blocker Groups

Variable:	N	Atenolol	Metoprolol Succinate	Metoprolol Tartrate	P-Value for Difference (one way ANOVA or Fischer's Exact Test)
		184	87	243	
		Mean (SD) or Number (%)	Mean (SD) or Number (%)	Mean (SD) or Number (%)	
Demographics:					
	Age (years)	68.0 (11.6)	68.5 (10.2)	69.2 (10.5)	0.55
	Male gender	176 (95.7%)	86 (98.9%)	237 (97.5%)	0.34
	Height (cm)	174.2 (7.9)	173.3 (8.5)	174.0 (7.9)	0.65
	Weight (kg)	94.4 (24.2)	89.0 (18.3)	90.4 (19.1)	0.07
	Body Surface Area	2.1 (0.29)	2.1 (0.23)	2.1 (0.23)	0.11
	Cardiothoracic/Vascular Surgery	20 (10.9%)	16 (18.4%)	58 (23.9%)	0.002
	Days since most recent Beta Blocker Rx	40.9 (25.0)	38.0 (25.5)	41.5 (25.0)	0.54
Comorbid Condition:					
	Coronary Artery Disease	85 (46.2%)	56 (64.4%)	160 (65.8%)	<0.001
	Congestive Heart Failure	21 (11.4%)	19 (21.8%)	50 (20.6%)	0.02
	Atrial Fibrillation	24 (13.0%)	18 (20.7%)	57 (23.5%)	0.02
	Hypertension	177 (96.2%)	83 (95.4%)	219 (90.1%)	0.04
	Diabetes Mellitus	78 (42.4%)	35 (40.2%)	110 (45.3%)	0.69
	Peripheral Vascular Disease	61 (33.2%)	27 (31.0%)	100 (41.2%)	0.12
	Kidney Disease	14 (7.6%)	6 (6.9%)	35 (14.4%)	0.04
	Psychiatric Disorder	84 (45.7%)	28 (32.2%)	94 (38.7%)	0.09
	Substance Abuse	44 (23.9%)	17 (19.5%)	56 (23.1%)	0.73
	Cerebrovascular Disease	36 (19.6%)	18 (20.7%)	55 (22.6%)	0.75
Anti-hypertensive Medication:					
	Antianginal	13 (7.1%)	9 (10.3%)	38 (15.6%)	0.02
	ACE-Inhibitor or ARB	62 (33.7%)	33 (37.9%)	78 (32.1%)	0.6
	Calcium Channel Blocker	43 (23.4%)	9 (10.3%)	46 (18.9%)	0.04
	Thiazide Diuretic	45 (24.5%)	10 (11.5%)	37 (15.2%)	0.01

Variable:	N	Atenolol Mean (SD) or Number (%)	Metoprolol Succinate Mean (SD) or Number (%)	Metoprolol Tartrate Mean (SD) or Number (%)	P-Value for Difference (one way ANOVA or Fischer's Exact Test)
Presenting Heart Rate:					
Primary Care SBP (mmHg)		132.3 (16.5)	130.4 (16.0)	132.4 (18.4)	0.63
Primary Care DBP (mmHg)		74.0 (12.7)	73.4 (10.5)	73.4 (13.1)	0.86
Primary Care Heart Rate (beats/min)		72.5 (14.9)	74.3 (12.9)	74.3 (15.7)	0.42
DOS SBP (mmHg)		136.4 (19.9)	137.6 (17.5)	137.1 (21.7)	0.89
DOS DBP (mmHg)		74.4 (10.8)	75.7 (10.0)	75.2 (11.3)	0.61
DOS Heart Rate (beats/min)		66.9 (12.1)	72.7 (12.7)	71.4 (14.2)	<0.001

ACE=Angiotensin Converting Enzyme; ARB=Angiotensin Receptor Blocker; SBP & DBP =Systolic & Diastolic Blood Pressure; DOS=Day of Surgery.