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Risk of Emergent Bradycardia Associated with Initiation of Immediate- or Slow-Release Metoprolol

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Abstract

Objectives—To estimate and compare the risk of emergent bradycardia associated with initiation of immediate-release (IR) and slow-release (SR) formulations of metoprolol.

Design—Retrospective analysis of administrative claims data.

Data Source—State of California Medicaid program (Medi-Cal) claims database.

Patients—A total of 31,574 adults initiating metoprolol between May 1, 2004, and November 1, 2009, without a pharmacy claim for a beta blocker within the previous 6 months of metoprolol initiation; patients with a primary or secondary diagnosis of symptomatic bradycardia, pacemaker, or implantable cardioverter-defibrillator placement before metoprolol initiation were excluded.

Measurements and Main Results—The study outcome was the time to first occurrence of emergent bradycardia, measured at an emergency department visit or hospitalization due to diagnosis of symptomatic bradycardia, after metoprolol initiation. We calculated the incidence and compared the risk of emergent bradycardia by using a proportional hazards model that included the metoprolol formulation with adjustment for total daily metoprolol dose and the use of other medications as time-varying covariates, as well as demographics and comorbidities. Among 31,574 patients initiating metoprolol, 18,516 (58.6%) initiated the IR formulation. The incidence of emergent bradycardia was 19.1 per 1000 person-years overall but was nearly twice as common in patients using the IR versus the SR formulation (24.1 per 1000 person-years in the IR group vs. 12.9 per 1000 person-years in the SR group; unadjusted hazard ratio [HR] 1.81; 95% CI 1.28-2.56). Adjustment for other medications also associated with symptomatic bradycardia (cytochrome P450 2D6 inhibitors, class I or III antiarrhythmics, and atrioventricular node–blocking agents), metoprolol dose, and other participant characteristics somewhat attenuated the association (adjusted HR 1.48, 95% CI 1.03-2.13).

Conclusion—The risk of emergent bradycardia associated with metoprolol initiation was higher with the IR formulation than the SR formulation, although the absolute risk was low.

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Keywords

metoprolol; oral; formulation; bradycardia

Metoprolol is the most widely prescribed oral beta blocker in the United States. In 2008, its prescription volume exceeded 68 million, making it the third most widely prescribed drug.[1] It has various indications including hypertension, angina, and myocardial infarction.

Bradycardia is a potentially serious adverse effect of metoprolol. Its incidence in large clinical trials is low, ranging from 0.8-9%.[2,3] Despite widespread use of the drug, however, the incidence in clinical practice outside of controlled experimental settings is unknown. Metoprolol reduces heart rate by antagonizing $beta_1$ receptors in the heart. Importantly, the degree of heart rate reduction positively correlates with the blood concentrations of metoprolol.[4-6] Thus, patients with elevated metoprolol blood concentrations may have an increased risk of bradycardia.

Two oral formulations of metoprolol are available: immediate release (IR; metoprolol tartrate) and slow release (SR; metoprolol succinate). Because of the different release kinetics, the IR formulation is usually administered twice a day versus once a day for the SR formation. In clinical practice, they are interchanged based on a total daily dose. For example, the IR formulation 50 mg twice daily is commonly interchanged with the SR 100 mg once daily. However, the two formulations have different pharmacokinetics, which may produce different pharmacodynamics including the degree of heart rate reduction.[7-9]

Thus, the objective of the study was to estimate and compare the risk of emergent bradycardia, measured at emergency department visits or hospitalizations due to bradycardia, associated with initiation of the two formulations of metoprolol (IR and SR) used in routine clinical practice.

Methods

Study Design and Data Source

In this retrospective analysis of administrative claims data, we used the State of California Medicaid program (Medi-Cal) claims database. Medi-Cal, which had over 8 million beneficiaries for at least one month between 2007 and 2008, provides insurance for persons with low income or disabilities in the State of California. The Medi-Cal claims database contains inpatient and outpatient administrative and pharmacy claims data including age, sex, race-ethnicity, first and last dates of Medi-Cal enrollment, claim types, dates of service, procedures, primary and secondary diagnoses, emergency department visits, drugs dispensed, national drug code numbers, units dispensed, and the number of days of a drug supply.

The study was approved by the Committee for the Protection of Human Subjects and the Data and Research Committee in the Department of Health Care Services in the State of California as well as the Committee for Human Research at the University of California San Francisco.

Study Sample

Patients aged ≥ 18 years old who were continuously enrolled in the Medi-Cal program for at least 6 months and had an oral metoprolol claim between May 1, 2004, and November 1, 2009, were included. Patients were a priori excluded if they were a Medicare beneficiary; had a beta blocker claim 6 months before the first metoprolol claim; had a diagnosis of

symptomatic bradycardia or pacemaker placement at least 6 months before the first metoprolol claim; had a diagnosis of hypothyroidism, hyperthyroidism, or ventricular fibrillation, or implantable cardioverter-defibrillator placement at least 6 months before the first metoprolol claim and the last day of metoprolol therapy; or had a thyroid hormone or antithyroid drug claim 30 days before the first metoprolol claim and 30 days after the last day of metoprolol therapy. The last day of metoprolol therapy was calculated by adding the number of days of the supply of the last metoprolol claim to the date of the last metoprolol claim. Diagnoses of symptomatic bradycardia, hypothyroidism, hyperthyroidism, ventricular fibrillation, and placement, revision, or check-up of the pacemaker or implantable cardioverter-defibrillator were identified with the *International Classification of Diseases, Ninth Revision* (ICD-9) codes (see Supplement for listing of specific ICD-9 codes used in the analysis). Use of a thyroid hormone and antithyroid drug was identified by searching for a pharmacy claim on the corresponding drugs (see Supplement). Patients with a total daily metoprolol dose of either < 6.25 mg or > 450 mg were also excluded because the 25 mg tablet of metoprolol is the lowest strength available, and the current maximum approved daily dose of metoprolol is 450 mg.[10] The follow-up time began at the time of the first metoprolol claim.

Study Outcome

The study outcome was the time to first occurrence of an emergency department visit or hospitalization due to symptomatic bradycardia as a primary diagnosis identified by ICD-9 codes (sinus node dysfunction, 427.81; sinus bradycardia, 427.89; atrioventricular block, 426.x).

Metoprolol Use

The metoprolol formulation (IR versus SR) was the primary predictor of the study outcome. To account for the effect of metoprolol dose on the study outcome, we adjusted for total daily metoprolol dose calculated according to the following formula: total daily dose = tablet strength dispensed × number of tablets dispensed ÷ number of days of supply.

Total daily metoprolol doses at the time of the study outcome or censoring were also grouped into four ranges based on the distribution of the total daily dose in the study sample: ≤ 37.5 mg/day, > 37.5 mg/day and ≤ 75 mg/day, > 75 mg/day and ≤ 125 mg/day, and > 125 mg/day.

Potential Confounders

The age at the time of the first metoprolol claim was calculated. Race-ethnicity was categorized as Caucasian, Hispanic, African-American, Asian, other, and unknown according to the race-ethnicity information in the database. Comorbidity data on hypertension, diabetes mellitus, coronary artery disease, heart failure, and atrial fibrillation were obtained by searching for primary and secondary diagnoses with the corresponding ICD-9 codes and claims on drugs for the treatment of comorbidities before the first metoprolol claim and 30 days after the last day of metoprolol therapy. Total daily metoprolol dose was also considered as a potential confounder.

Use of non-metoprolol drugs—an atrioventricular (AV) node–blocking agent, a Vaughan Williams classes I and III antiarrhythmics, a cytochrome P450 (CYP) 2D6 inhibitor, a cholinergic agent for Alzheimer's disease, a drug that increases heart rate, or an ophthalmic beta blocker—was defined as any corresponding drug claim between 30 days before the first metoprolol claim and 30 days after the last day of metoprolol therapy. Non-metoprolol oral beta blockers were included in AV node–blocking agents. The list of CYP2D6 inhibitors, which can increase metoprolol blood concentrations, was obtained from the Indiana

University Clinical Pharmacology P450 Drug Interaction Table.[5,11-14] The supplement contains the list of the drugs used in this study.

Statistical Analysis

We described patients initiating metoprolol by formulation type (SR and IR). The unpaired t-test, Wilcoxon rank sum test, and Chi-squared test were used as appropriate. We analyzed cumulative incidence, incidence rates (per 1000 person-years), and time to event for the study outcome. Time to event was estimated by the Kaplan-Meier method and compared between the SR and IR groups by the log-rank test. Patients were censored at the time of the first occurrence of one of the following: they disjoined the Medi-Cal program; they did not have a claim on the same formulation of metoprolol within 5 days after the refill due date; or November 1, 2009 (the end date of the study). The Cochran-Armitage test was used to check a significant trend between the study outcome and the total daily metoprolol dose ranges. A Cox proportional hazard regression analysis was performed to model the study outcome as a dependent variable with metoprolol formulation as an independent variable, with adjustments for potential confounders. In this model, total daily metoprolol doses and the use of non-metoprolol drugs were treated as time-varying covariates. Because of the small number of study outcomes, the backward elimination method was also used to select a model. Interactions between the metoprolol formulation and potential confounders were tested in a full model. The linearity of total daily metoprolol doses was checked by adding a quadratic term. The proportional hazards assumption was checked by adding to a full model an interaction term between each explanatory variable and time. As an exploratory analysis, cumulative hazard ratios were computed by days after metoprolol initiation.

Four sets of sensitivity analyses were conducted. First, as an alternate method for adjustment, we constructed a propensity score including baseline covariates (age, sex, race-ethnicity, and comorbidities) using logistic regression and used this score in lieu of the baseline covariates in the Cox model. Second, syncope was included as part of the study outcome because it can be caused by symptomatic bradycardia. In this analysis, patients with a primary or secondary diagnosis of syncope, hypotension, or seizure and/or with a pharmacy claim on drugs used for syncope or seizure before the first claim on metoprolol were excluded. In addition to the confounders of the emergent bradycardia, use of diuretics, vasodilators, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, direct renin inhibitors, and drugs used for the treatment of syncope were considered as potential confounders (see Supplement for a full list of the drugs). A Cox proportional hazard regression analysis was performed to model the first occurrence of emergent bradycardia or syncope as a dependent variable with metoprolol formulation as an independent variable, with adjustments for potential confounders. Third, a multivariable Cox proportional hazards regression analysis was performed only in patients without a diagnosis of heart failure because heart failure was significantly more prevalent in the IR group than in the SR group, and heart failure may be associated with symptomatic bradycardia.[15] Finally, a multivariable logistic regression analysis limited to patients who had the study outcome during the first month of metoprolol therapy and had the first metoprolol claim with at least 30 days of a supply was performed. In this analysis, metoprolol formulation was included in a multivariable logistic regression model that used the cumulative incidence of an emergency department visit or hospitalization due to bradycardia during the first month as a dichotomous outcome, and with adjustments for potential confounders. SAS statistical software, version 9.1 (SAS Institute Inc., Cary, NC) was used for all analyses. A p value of less than 0.05 was considered to indicate a statistically significant difference.

Results

A total of 31,574 patients were included in the analysis. Of these patients, 13,058 (41.4%) were in the SR group and 18,516 (58.6%) were in the IR group (Table 1). Of note, the IR group had a significant higher proportion of patients with a diagnosis of heart failure and atrial fibrillation as well as of the use of an AV node–blocking agent and class I or III antiarrhythmic agent than the SR group. The study sample was enrolled in Medi-Cal for a median of 28 months (range 7-67 months). The SR group had a significantly longer enrollment than the IR group (median 28 months vs. 25 months, $P < 0.001$).

The duration of the metoprolol therapy was relatively short (median 58 days; range 1-1825 days). The SR group had a slightly longer duration than the IR group (median 60 days [range 2-1710 days] vs. median 52 days [range 1-1825 days], $P<0.001$). At the time of the censoring or study outcome, both groups had a median total daily metoprolol dose of 50 mg (range 6.25-400 mg in the SR group vs. 6.25-450 mg in the IR group, $P<0.001$) for a median of 30 days (range 0-1100 days in the SR group vs. 1-1418 days in the IR group, $P<0.001$).

The study outcome developed in 154 patients (Table 2). Emergency department visits for emergent bradycardia were three times as common as hospitalizations for the same condition. The SR group had a significantly lower incidence of emergent bradycardia than the IR group (12.9 per 1000 person-years in the SR group vs. 24.1 per 1000 person-years in the IR group, $P=0.0037$). This difference was primarily due to the difference in emergency department visits ($P=0.0013$).

The Kaplan-Meier analysis showed a significant difference in the study outcome between the groups (Figure 1). In both the unadjusted and adjusted proportional hazards regression analyses, the metoprolol formulation was significantly associated with the risk of the study outcome (Table 3). The use of the IR formulation was associated with a 48% increase in the risk of the study outcome compared with the use of the SR formulation in a fully adjusted model (HR = 1.48; 95%CI: 1.03-2.13), which is somewhat attenuated from the unadjusted estimate (HR = 1.81; 95%CI: 1.28-2.56). We found no significant interaction between potential confounders and formulation, and no deviations from the proportional hazards assumption.

The incidence of emergent bradycardia significantly increased as total daily metoprolol doses at the time of an event or censoring increased (Figure 2). However, there was no significant interaction between metoprolol dose range and formulation in a fully adjusted model ($p=0.51$).

During the first 60 days after metoprolol initiation, the use of the IR formulation was associated with a 70% increased risk of emergent bradycardia compared with that of the SR formulation (Table 4; HR 1.70; 95% CI 1.06-2.71). After this period, the risk difference between the formulations was attenuated.

The results of the sensitivity analyses were not qualitatively different from the main results. In a model adjusting for propensity scores, the use of the IR formulation was associated with a 50% higher risk than that of the SR formulation (HR 1.50; 95% CI: 1.04-2.16). When syncope was included as part of the study outcome, a total of 28,285 patients (57.8% in the IR group, 42.2% in the SR group) were included in the analysis, with 268 patients who had emergent bradycardia or syncope (eTable 1). In this analysis, the use of the IR formulation was associated with a 40% increased risk of emergent bradycardia or syncope compared with the use of the SR formulation (eTable 2; HR 1.40; 95% CI: 1.07-1.83). When the analysis was limited to patients without a diagnosis of heart failure or to patients with the first metoprolol claim with at least 30 days of supply, the results were unchanged (patients

without heart failure: HR 1.62, 95% CI 1.04-2.53; patients with at least 30 days of supply: OR 1.82, 95% CI 1.06-3.14).

Discussion

To our knowledge, this is the first comparative effectiveness study estimating absolute and relative risks of emergent bradycardia associated with initiation of two oral metoprolol formulations (IR and SR) used in routine clinical practice. In this retrospective analysis of Medi Cal claims data, we found that the overall absolute risk of emergent bradycardia associated with metoprolol therapy in routine clinical practice was low (19.1 per 1000 person-years), but that there is a 48% increase in that risk with use of the IR formulation compared with the SR formulation. Of note, the difference in risk of the emergent bradycardia between the IR and SR formulations was larger during the first 60 days after metoprolol initiation compared with the later period (HR 1.70 vs. 1.48), suggesting that patients newly starting the IR formulation should be more carefully monitored during the first 60 days of the IR initiation.

Although the incidence rate of adverse drug events is usually higher in clinical practice than that in a clinical trial, our incidence rate (19.1 per 1000 person-years) was lower than that of the previous quantitative overview of 9 large, randomized, clinical trials in patients with heart failure (38 per 1000 person-years).[16] The fact that some of these clinical trials did not require an emergency department visit or hospitalization as part of their definitions of adverse bradycardia may help explain why the rate in that study is higher than the rate we found. The trials also used different beta blockers such as carvedilol and bisoprolol. Finally, the characteristics of our study sample, which was relatively young and had fewer structural heart diseases, could have contributed to the lower incidence rate. Overall, our data suggest that emergent bradycardia associated with the use of metoprolol, the most prescribed beta blocker in the United States, may not be common in clinical practice.

Our results are in contrast to those of a randomized trial reporting no significant difference in the degree of heart rate reduction between the two metoprolol formulations in 100 patients with hypertension.[17] Since it had a small sample size and excluded patients at a high risk of metoprolol-related bradycardia such as those with heart failure, however, our study may have better assessed the risk of bradycardia between the metoprolol formulations.

In our study, there was a significant trend between total daily metoprolol dose and the incidence of emergent bradycardia (Figure 2). At the same daily dose, the metoprolol IR formulation produced a 2.4-2.8 fold higher peak blood concentration than the SR formulation.[7-9] Since the degree of heart rate reduction by metoprolol is positively correlated with metoprolol blood concentrations, the IR formulation would decrease heart rate to a greater degree than the SR formulation at the time of peak concentration.[5,6] Indeed, the administration of the metoprolol IR formulation of 50 mg twice a day reduced heart rate by 19.1% from the baseline compared with 13.4% with the SR formulation of 100 mg daily.[7] Thus, the difference in blood concentrations between the formulations at the same daily dose may have lead to a significant difference in the risk of emergent bradycardia in our study. Because only 8.3% of the study population received a total daily metoprolol dose of >125 mg/day at the time of the study outcome or censoring, however, we were not able to fully assess dose-response relationship at higher metoprolol doses (>125 mg/day).

Our data have important clinical implications. The metoprolol SR formulation has more convenient dosing and is the only metoprolol formulation approved for the treatment of heart failure. Since our data also suggest that the SR formulation may be safer than the IR formulation, the SR formulation may be preferable particularly for patients at a high risk of

emergent bradycardia, such as those with heart failure who are also taking a CYP2D6 inhibitor or an AV node–blocking agent (eTable 3). For patients who are uninsured or need better heart rate control, the IR formulation is less costly and provides higher blood concentrations. Given the increased risk of emergent bradycardia with the IR formulation, heart rate should be monitored closely for patients who have a low resting heart rate, particularly during the first 60 days after the SR formulation is switched to the IR formulation.

Our study has several limitations. First, our study relies on administrative claims data. Claims data do not provide information on potential clinical predictors of emergent bradycardia episodes such as heart rate, *CYP2D6* genotypes, over-the-counter medication use, and the patients' drug adherence. Thus, our data collection did not account for many important factors that may impact on the study results. In addition, population is relatively young, which could have influenced our study results. Given the difference in the indications of the two formulations, confounding by indication may have influenced our study results. In particular, confounders associated with an increased risk of emergent bradycardia, such as heart failure, were significantly more prevalent in the IR group than in the SR group. We were unable to rebalance the groups with our statistical methods. Instead, we attempted to control for confounding by using both standard adjustment methods and propensity scores as well as by limiting the analysis to patients without heart failure, but the sparse covariate information in this dataset limits this approach to some degree. It is possible that an unmeasured confounder could account for our findings, but to do so, the confounder would have to be very strongly associated with both the predictor and the outcome. Adapting prior methods for use in our study, we estimate that for a common confounder (overall prevalence of 50%), the association between the confounder and both the exposure and the disease must still be quite strong (odds ratio of 4 for each)[18]; this could occur, for example, if the confounder is present in 64% of the IR group and 30% of the SR group, and the event rate (proportion with an event) is about 0.008 vs. 0.002 when the confounder is present vs. absent. If the confounder is less common (overall prevalence of 10%), the associations would have to be stronger (odds ratios of 6 for each). Although we allowed only 5 days between metoprolol refill dates, this may be too long given the short half life of metoprolol (6-8 hours).

In our sensitivity analysis, by limiting to patients with at least 30 days of supply of the first metoprolol claim, however, our results were unchanged. Inaccurate coding of administrative claims can result in misclassification of diagnoses and study outcomes.[19] Our study could have missed shortness of breath and lightheadedness due to bradycardia. This inaccurate coding may have contributed to the reduced rates of bradycardia in our study compared to those in other studies.[16] When syncope was included as part of the study outcome, however, the results were not substantially different from those excluding syncope.

Second, we excluded pacemaker implantation as part of the study outcome because it was difficult to distinguish between elective and urgent pacemaker implantation by using ICD-9 codes. This exclusion may have resulted in underestimation of the study outcome. Third, we observed only a short median duration of metoprolol therapy, which may have led to the underestimation of the study outcome. Finally, comorbidities identified by the use of drugs may not have been accurate because some drugs have multiple indications. For example, amiodarone is indicated for both atrial fibrillation and ventricular fibrillation.

Conclusion

The use of the metoprolol IR formulation instead of the SR formulation was associated with an increased risk of serious bradycardic events requiring emergency care or hospitalization, although the absolute risk was low.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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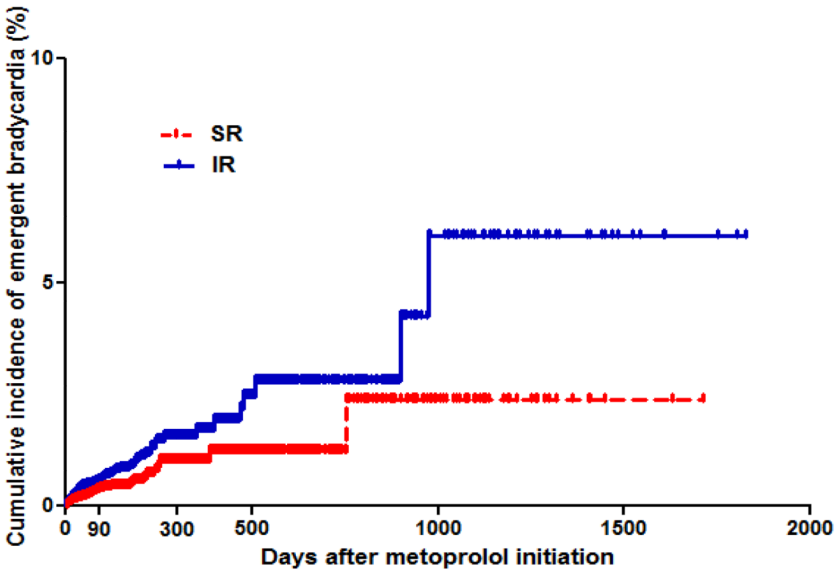

Number at risk

SR	13058	4957	745	266	38	2
IR	18516	5717	880	311	48	8

Figure 1.

Kaplan-Meier estimates of the risk of emergent bradycardia by oral metoprolol formulation (log-rank P= 0.0006).

Abbreviations: SR, slow-release; IR, immediate-release.

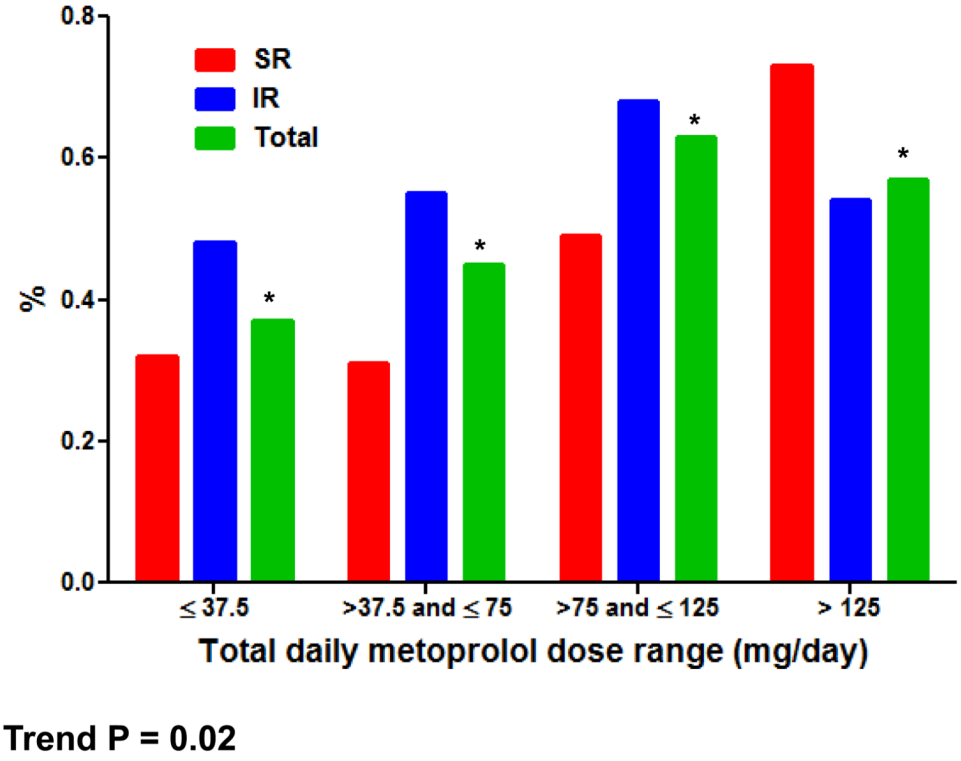

Figure 2.
Incidence of emergent bradycardic events by total metoprolol daily dose range (*trend P= 0.02).
Abbreviations: SR, slow-release; IR, immediate-release.

Table 1
Baseline Demographic and Clinical Characteristics of the Study Patients

Characteristic	All Patients (n=31,574)	Metoprolol SR Group (n=13,058)	Metoprolol IR Group (n=18,516)	P-value
Proportion of all patients		41.4%	58.6%	
Age (yrs), mean ± SD	56.1 ± 12.7	56.4 ± 12.8	55.9 ± 12.7	0.001
Male	46.2%	43.0%	48.4%	<0.001
Race-ethnicity				<0.001
Caucasian	34.7%	39.4%	31.5%	
Hispanic	27.0%	21.6%	30.8%	
African-American	15.0%	11.7%	17.3%	
Asian	8.7%	10.6%	7.4%	
Other	9.0%	11.1%	7.5%	
Unknown	5.7%	5.7%	5.7%	
Comorbidities				
Hypertension	88.0%	88.0%	88.0%	0.94
Diabetes mellitus	39.2%	35.5%	41.8v	<0.001
Coronary artery disease	32.0%	30.1%	33.3%	<0.001
Heart failure	15.7%	12.7%	17.8%	<0.001
Atrial fibrillation	6.7%	5.1%	7.7%	<0.001
Use of non-metoprolol drugs				
AV node–blocking agent[a]	17.5%	14.7%	19.5%	<0.001
Non-metoprolol oral beta blocker[b]	3.2%	3.1%	3.2%	0.65
Class I or III antiarrhythmic[c]	1.7%	1.4%	1.9%	0.005
CYP2D6 inhibitor[d]	42.6%	45.1%	40.8%	<0.001
Cholinergic agent for Alzheimer's disease[e]	1.4%	1.7%	1.2%	<0.001
Drug that increases heart rate[f]	3.4%	4.8%	2.4%	<0.001
Ophthalmic beta blocker[g]	1.1%	1.2%	1.1%	0.40

Abbreviations: SR, slow release (metoprolol succinate); IR, immediate release (metoprolol tartrate); ICD, implantable cardioverter defibrillator; AV, atrioventricular; CYP, cytochrome P450.

[a] Includes verapamil, diltiazem, digoxin, clonidine, and non-metoprolol oral beta blockers.

[b] Includes acebutolol, atenolol, bisoprolol, carvedilol, labetalol, nebivolol, nadolol, pindolol, penbutolol, and propranolol.

[c] Includes disopyramide, quinidine, procainamide, mexiletine, flecainide, propafenone, amiodarone, sotalol, dofetilide, and dronedarone.

[d] Includes fluoxetine, paroxetine, bupropion, cinacalcet, duloxetine, sertraline, terbinafine, cimetidine, ritonavir, celecoxib, chlorpheniramine, chlorpromazine, citalopram, clemastine, clomipramine, diphenhydramine, doxepin, escitalopram, haloperidol, hydroxyzine, methadone, metoclopramide, midodrine, perphenazine, propoxyphene, ranitidine, ticlopidine, and tripelennamine.

[e] Includes donepezil, galantamine, and rivastigmine.

[f] Includes phenylephrine, pseudoephedrine, amphetamine, methylphenidate, and modafinil.

[g] Includes betaxolol, carteolol, levobunolol, metipranolol, and timolol.

Table 2

Incidence of Emergent Bradycardia by Metoprolol Formulation[a]

Metoprolol Formulation Group	Emergency department visits			Hospitalizations			Total events		
	No. of Patients	% of Patients[b]	No./1000 person-years	No. of Patients	% of Patients[b]	No./1000 person-years	No. of Patients	% of Patients[b]	No./1000 person-years
SR (n=13,058)	32	0.25	9.0	14	0.11	3.9	46	0.35	12.9
IR (n=18,516)	87	0.47	19.4	21	0.11	4.7	108	0.58	24.1
Both SR and IR (n=31,574)	119	0.38	14.8	35	0.11	4.3	154	0.49	19.1

Abbreviations: SR, slow release (metoprolol succinate); IR, immediate release (metoprolol tartrate).

[a] Emergent bradycardia was defined as first occurrence of an emergency department visit or hospitalization after initiation of metoprolol.

[b] The proportion of patients with the study outcome during the entire study period.

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Table 3

Unadjusted and adjusted hazard ratios of emergent bradycardia between the two metoprolol formulations.

Metoprolol Formulation Group	Hazard Ratio (95% CI)			
	Unadjusted	Adjusted		
		Model 1[a]	Model 2[b]	Model 3[c]
SR	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
IR	1.81 (1.28-2.56)	1.63 (1.13-2.36)	1.51 (1.04-2.18)	1.48 (1.03-2.13)

Abbreviations: SR, slow-release; IR, immediate-release, CI, confidence interval.

[a] Adjusted for age, sex, race-ethnicity, and total daily metoprolol dose.

[b] Adjusted for age, sex, race-ethnicity, total daily metoprolol dose, atrial fibrillation, coronary artery disease, diabetes mellitus, hypertension, and heart failure.

[c] Adjusted for age, sex, race-ethnicity, total daily metoprolol dose, atrial fibrillation, coronary artery disease, diabetes mellitus, hypertension, heart failure, and use of a class I or class III antiarrhythmic, an atrioventricular node–blocking drug, a cytochrome P450 2D6 inhibitor, an ophthalmic beta blocker, a cholinergic drug for Alzheimer's disease, and a drug that may increase heart rate.

Table 4

Occurrence of emergent bradycardia by number of days after metoprolol initiation.

Days after metoprolol initiation	No. (%) of events			Cumulative Hazard Ratio* (95% CI)
	All Patients (n=31,574)	Metoprolol SR Group (n=13,058)	Metoprolol IR Group (n=18,516)	
0-15	50 (0.16)	13 (0.10)	37 (0.20)	1.86 (0.95-3.65)
15-30	30 (0.10)	8 (0.06)	22 (0.12)	1.81 (1.06-3.08)
30-60	21 (0.07)	6 (0.05)	15 (0.08)	1.70 (1.06-2.71)
60-90	14 (0.04)	7 (0.05)	7 (0.04)	1.42 (0.93-2.18)
90-365	31 (0.10)	10 (0.08)	21 (0.11)	1.39 (0.96-2.01)
>365	8 (0.03)	2 (0.02)	6 (0.03)	1.48 (1.03-2.13)

Abbreviations; SR, slow-release; IR, immediate release formulation; CI, confidence interval.

*IR vs. SR (reference); adjusted for age, sex, race-ethnicity, total daily metoprolol dose, atrial fibrillation, coronary artery disease, diabetes mellitus, hypertension, heart failure, and use of a class I or class III antiarrhythmic, an atrioventricular node–blocking drug, a cytochrome P450 2D6 inhibitor, an ophthalmic beta blocker, a cholinergic drug for Alzheimer's disease, and a drug that may increase heart rate.