TO DETERMINE WHETHER THE SURVIVAL BENEFITS OF β-BLOCKADE IN ACUTE CORONARY EVENTS IS ASSOCIATED WITH THE MAGNITUDE OF HEART RATE REDUCTION OR IS SIGNIFICANTLY BETTER BELOW A GIVEN TARGET HEART RATE

by

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ABSTRACT

Background*:* Atherosclerotic coronary artery disease is the leading cause of morbidity and mortality in men and women in the United States. Beta-blocker therapy is widely used in patients after acute coronary disease to lower heart rate. To date, there fails to be evidence-based clinical trials demonstrating the ideal target heart rate and survival benefits after initiation of beta-blockers in patients presenting with ACS.

Objective*:* To determine whether the survival benefits of β-blockade in acute coronary events is associated with the magnitude of heart rate reduction or is significantly better below a given target heart rate.

Methods*:* A retrospective chart review was conducted at St. Johns Hospital in 434 patients over a two-year period, for ACS (STEMI and NSTEMI) and subsequently treated with beta-blockers. Beta-blocker usage, heart rate reduction and adverse outcomes (MACE) in these patients were evaluated, and mortality data were obtained from the Social Security Administration database.

Results*:* Categorical variables were analyzed by Chi-squared tests. Continuous variables were analyzed using ANOVA and subsequently, pair-wise student tests. Predictors of MACE were analyzed using logistic regression analysis.

Conclusions*:* In patients with Acute Coronary Syndromes (ACS), both STEMI and NSTEMI, lower discharge resting heart rate (RHR) conferred a decrease in mortality and morbidity endpoints at 6 months. Further studies are needed to confirm the effects of low RHR and mortality, morbidity, benefits in ACS patients with beta-blockers usage to a target of < 65 beats per minute prior to discharge.

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CHAPTER 1: INTRODUCTION AND BACKGROUND

Introduction and Background

Atherosclerotic coronary artery disease is the leading cause of morbidity and mortality in men and women in the United States[8], and its prevalence makes it a public health problem worldwide[13]. Despite modern therapy including intensive pharmacological treatment and interventional revascularization procedures, affected patients still suffer high event rates, including angina pectoris, myocardial infarction (MI), heart failure (HF) and cardiovascular death[20]. The American Heart Association estimated nearly 800,000 new acute coronary syndromes (ACS) and 500,000 recurrent events occurred in 2009[12]. Atherosclerosis or atherosclerotic coronary artery disease is a disease in which plaque builds up inside the arteries. Overtime, the plaque hardens and narrows the arteries. This limits the flow of oxygen-rich blood to the organs and other parts of the body[15]. Atherosclerosis can lead to serious problems including heart attack, stroke or even death. Heart attacks are divided into two types, according to their severity:

1) A STEMI-“ST segment elevation myocardial infarction” is the more severe type. In a STEMI, the coronary artery is completely blocked off by the blood clot, and as a result virtually all the heart muscle being supplied by the affected artery starts to die[19], and;

2) NSTEMI-"non-ST segment elevation myocardial infarction," is the less severe type. In a NSTEMI, the blood clot only partly occludes the artery, and as a result only a portion of the heart muscle being supplied by the affected artery dies[16].

The cornerstone of medical therapy for Acute Coronary Syndrome (ACS) is beta-blockers (BB) along with the use of anti-platelet medications, nitrates, and statins[10]. Beta-

1 adrenergic receptor blockers work to slow heart rate, which increases the diastolic time and improves coronary circulation, thus reducing cardiac work and myocardial oxygen demand. Beta-blocker therapy is widely used in patients after acute coronary disease to lower heart rate. It is presumed that by lowering heart rate, risk of subsequent heart attack will be decreased. This assumption is based on studies that demonstrated that decreased risk of death from heart disease is directly related to resting heart rate in healthy individuals[4, 18] and patients at high risk for acute coronary events[2]. For instance, acute beta blockade was significantly associated with lower hospital mortality in ST elevated myocardial infarction (STEMI) patients with and without reperfusion therapy[5]. The greatest benefit of acute beta-blocker treatment, as measured by the number needed to treat to save 1 life, was found in patients with a heart rate at presentation greater than or equal to 80 beats/min[5].

Similar studies have been conducted with heart failure patients. Guidelines recommend that patients with heart failure receive β-blockers in doses of proven efficacy, not with the goal of reaching a target heart rate. Nonetheless, in these studies, for every heart rate reduction of 5 beats/min with β-blocker treatment, a commensurate 18% reduction in the risk for death occurred.[14]

Guidelines from the American College of Cardiology (ACC) and other cardiology societies recommend that the resting heart rate be targeted at between 50 and 60 beats per minute on beta-blocker therapy. However, the ACC recommendation is not based on randomized clinical trials, rather expert opinion. Without firm evidence to guide them, each cardiologist sets their own target heart rates. To date, there fails to be evidence-based clinical trials demonstrating the ideal target heart rate after initiation of beta-

blockers in patients presenting with ACS. A pilot study was thus conducted in which we examined the outcomes of ACS patients on beta-blocker therapy.

Study Objectives

- To determine whether the survival benefits of β-blockade in acute coronary events is associated with the magnitude of heart rate reduction or is significantly better below a given target heart rate

Study Hypothesis

- Survival benefits of β-blockade in acute coronary events is directly associated with the magnitude of heart rate reduction and is significantly better below a given target heart rate

CHAPTER 2: REVIEW OF RELATED LITERATURE

Several studies have shown that beta-blockers are able to reduce total mortality and sudden cardiac death after MI, and the beneficial effects are in part associated to the reduction of HR[11]. Furthermore, a recent meta-regression of randomized clinical trials of beta-blockers and calcium channel blockers in post-acute MI patients strongly suggest that the beneficial effects of these agents are proportionally related to the reduction of resting HR[3]. Additionally it was shown in more recently in randomized controlled trials of beta-blockers in HF due to left ventricular systolic dysfunction that there is a close relation between all-cause change in HR and change in left ventricular ejection fraction[7].

Messerli has recently described an inverse relationship between HR reduction with beta-blockers and cardiovascular end points in patients with hypertension[1]. However, this cannot be explained solely by pharmacological HR slowing, as beta-blockers not only reduce HR, but also have a number of other effects.

On the basis of the results of 10 randomized controlled trials, Kjekshus had observed that a correlation might exist between beta-blocker-induced reduction in resting HR and reduction in total mortality[9].

In a prospective study of 50,100 healthy people (followed for 18 years), they found, for each increment of 10 bpm increase HR at rest, risk of death from Ischemic heart disease was 18% higher in women and 10% higher in men[6].

In another prospective study of 5,139 healthy workers (followed for 5 years), they found people with decreased RHR, (change from Heart rate (HR) at examination and HR from inclusion) had a 14% decreased mortality risk, and people with increased RHR had a 19% increased mortality risk[18].

Lastly, In a meta analysis conducted on 19,209 heart failure patients, the authors showed that for every heart rate reduction of 5 beats/min with a β – blocker treatment, a commensurate 18% reduction in the risk for death occurred; however, there was no survival benefit with increased doses of beta-blocker[5].

CHAPTER 3: RESEARCH DESIGN AND METHODOLOGY

Setting

St. John Providence Health System IRB approval was obtained to conduct the study at Providence and St. John Moross Hospital. The study was initiated at Providence and the study was expanded to include patients at St. John Moross. The data obtained from St. John Moross is shown in this thesis, but it will be been eventually combined with the Providence data for final statistical analysis and publication.

Study Design

This was a descriptive, retrospective study analyzing hospital medical records to extract data of subjects seen at St. John Providence Health System during the period of January 2007 to December 2009. The study was approved by the Institutional Review Board, which waived the need for patient consent.

Study Population

- 434 patients with Acute Coronary Syndrome (ACS) presented to St. John Moross Hospital were included in the analysis
- 212 ST Elevation Myocardial Infarction patients:
- 222 Non ST Elevation Myocardial Infarction patients (non-STEMI)
- All patients were subsequently treated with beta-blockers.

Inclusion/Exclusion Criteria

Subjects were included in the study if they were adult patients with ST elevation myocardial infarction (STEMI) or non-ST elevation myocardial infarction (NSTEMI) and who were subsequently treated with beta-blockers to control heart rate, either during Emergency Department admission or hospital stay. Subjects were excluded if they had presented initially with Cardiogenic shock, with Systolic Blood Pressure $\leq$ 90, with Heart rate $\leq$ 60, having contraindications to the use of beta-blockers, second or third degree heart block, active asthma, reactive airway disease, and if they were less than 18 years of age.

Data Collection

The Emergency Department's and the St. Johns Moross hospital's computerized records systems were utilized to identify subjects for this study. Patient charts were reviewed for demographics; risk factors; HR at presentation in ER; HR at Discharge; Medication list; diagnostic reports; and adverse events. Social Security Administration databases were examined to record any deaths that occurred during the study period.

Data Analysis

We utilized SPSS (SPSS Inc. version 13, Chicago, IL) and Microsoft Excel for data management and analysis. The co-investigator collected all data and a manual check was performed after collection of all data. The principal investigator completed a second manual check to review the accuracy of information by evaluating medical records, with information collected on data collection sheets. Means and proportions were compared with chi-square methods and t-tests. A p-value of less than 0.05 was

considered statistically significant. Categorical variables were analyzed by Chi-squared tests. Continuous variables were analyzed using ANOVA and subsequently, pair-wise student tests. Predictors of MACE were analyzed using logistic regression analysis.

CHAPTER 4: RESULTS

Patients were stratified based on resting heart rate (RHR) at discharge by quartiles as follows:

- Quartile 1: Lower –RHR below 67
- Quartile 2: RHR between 67 to 73
- Quartile 3: RHR between 74 to 81
- Quartile 4: Upper –RHR above 81

Patients in each quartile were analyzed to demonstrate adverse outcomes. Demographic factors that might predict outcomes (DM, HTN....) were evaluated by regression analysis for predictors of MACE.

Since Resting Heart Rate (RHR) variability is unavoidable –

- We tabulated the average of three to five readings at the given time, depending on the availability in the charts. We felt that this approach is acceptable considering clinical point of view as we depend on only one reading in the office.

Patient outcomes were outlined as follows –

- Primary end points: Major Adverse Cardiac Events (MACE) –all cause mortality, re-infarction or cardiac arrest
- Secondary end points: Cardiac death at 6 months, Length of stay and Ejection Fraction (EF)

The primary outcome (MACE) was found to be predicted by Discharge RHR alone. Moreover, analyzing the incidents of MACE demonstrated that lower the Quartile (Quartile 1, 12.9%), the lower the occurrence of MACE. Thus, low RHR predicts lack of

(MACE), and significant differences were seen between quartiles 1 and 4, shown in the Figure 1 below.

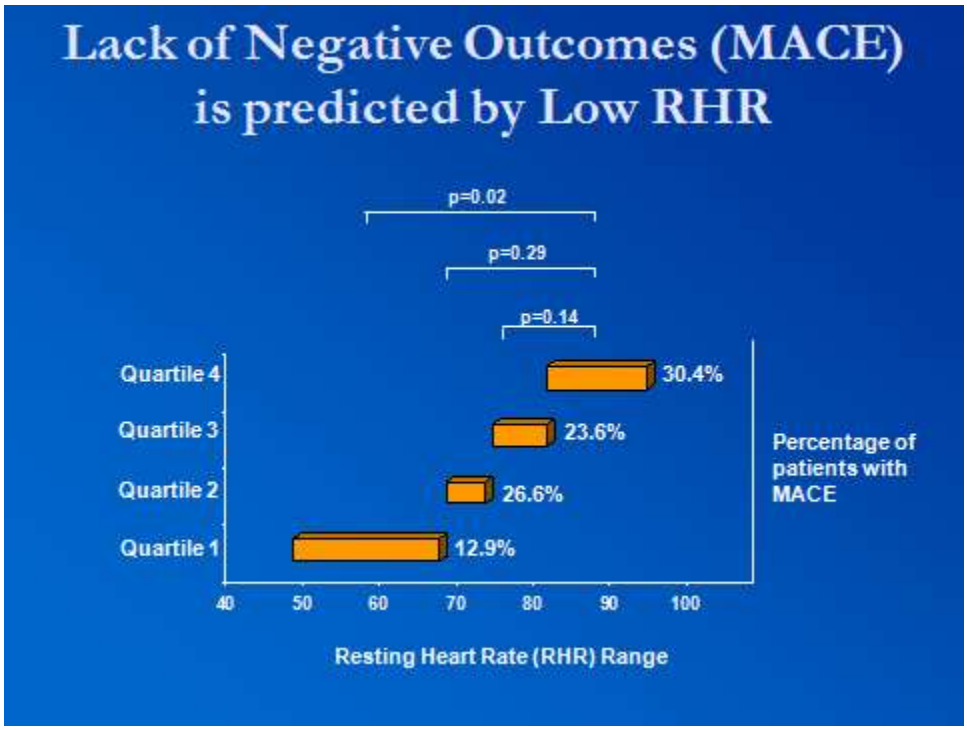

Figure 1. MACE in ACS patients stratified by RHR quartile.

The graph below depicts the calculation of the Odds Ratio for MACE in each quartile. Quartile 1 showed 56% reduction in the risk of MACE compared to all patients in the study (Figure 2).

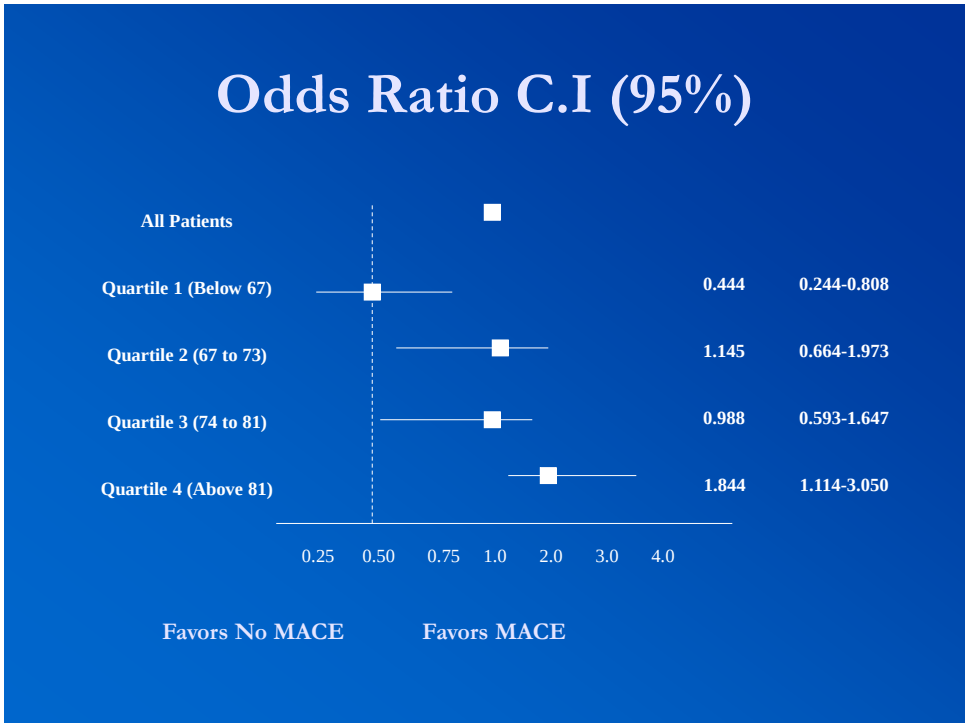

Figure 2. Odds Ratios for MACE in the patient population.

These outcomes are only relevant if there are no significant differences in the baseline characteristics in the patients being compared as concerns risk factors known to affect heart disease. Baseline demographic data for patients in all four quartiles showed no statistical differences. The data for quartiles 1 and 4 are shown in the Table 1 below.

Table 1. Baseline Demographics

	Quartile 1	Quartile 4	p value
Age	**60.4± 12.6**	**58.3 ± 14.1**	**0.26**
Race (% Caucasian)	**47.6 %**	**50%**	**0.85**
Gender (% male)	**75%**	**63.7%**	**0.21**
HTN	**64.7**	**81.4**	**0.27**
DM	**25.0**	**34.3**	**0.26**
Tobacco	**50.0**	**51.0**	**0.83**
Cholesterol	**64.7**	**57.8**	**0.35s**

The length of stay for the four quartiles shows that expected the patients with lower RHR, below 67 had a shorter length of stay compared to all other patients irrespective of the demographic data and co morbidities, Figure 3 below.

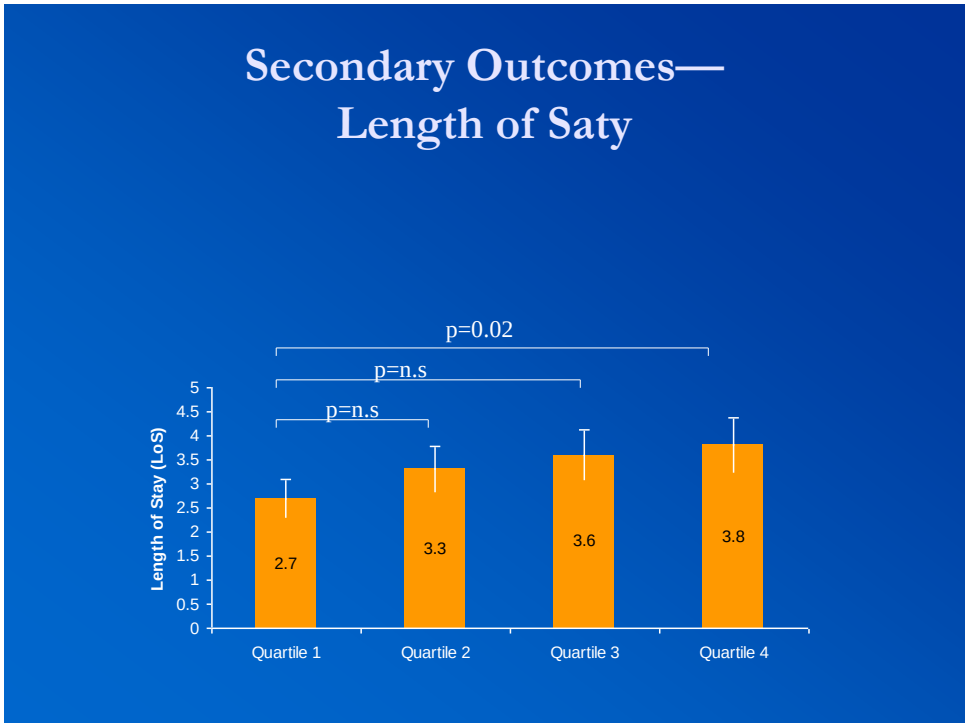

Figure 3. Length of stay for patients in the study.

CHAPTER 5: CONCLUSIONS

In patients with Acute Coronary Syndromes, both STEMI and NSTEMI, lower discharge RHR conferred a decrease in MACE and mortality at 6 months of follow up. Further studies are needed to confirm the effects of low RHR and mortality, morbidity, benefits in ACS patients with beta-blockers usage to a target of < 67 bpm prior to discharge.

CHAPTER 6: LIMITATIONS OF THE STUDY

Limitations of the study included the following: (a) Retrospective Analysis; (b) Small sample size; (c) number of treating physicians; (d) Absence of control group; (e) incomplete medical records excluded some subjects from contributing to this study; (f) Data collected from the charts; (g) Relatively small size; (h) shorter follow up duration.

Recommendations

In patients presenting with acute myocardial infarction to the hospital, beta-blockers should be used liberally and titrated to achieve a target heart rate below 67 upon discharge.

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Appendix 1: Data capture Sheet:

β-Blocker Usage Heart Rate Reduction and Outcomes in Patients With Acute Coronary Syndromes

1. **Patient name**
2. **Medical Record Number**
3. **Age**
4. **Gender**
5. **Race**
6. **Social Security Number**
7. **Medications and dosage**
8. **Hypertension**
9. **Diabetes Mellitus**
10. **Tobacco history**
11. **Hypercholesterolemia**
12. **Length of stay**
13. **Blood pressure: on presentation, on discharge, 3-6 months after discharge**
14. **Heart rate: on presentation, on discharge, 3-6 months after discharge**
15. **Ejection Fraction (EF)% on presentation**
16. **EF% at follow up**
17. **Death**
18. **MACE**
19. **Number of diseased vessels**
20. **Number of stents**
21. **Dissection and treatment**
22. **Shock**
23. **30 days mortality**
24. **360 days mortality**