Adherence of Beta-Blockers Post Myocardial Infarction

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OBJECTIVES

1) Briefly review the epidemiology, pathophysiology, diagnosis, and treatment of acute myocardial infarction
2) Discuss the importance of and recommendations for secondary prevention, especially with a beta-blocker
3) Evaluate beta-blocker utilization rates
4) Discuss medication adherence and common barriers
5) Investigate methods to increase adherence and improve patient outcomes

BACKGROUND INFORMATION¹⁴

EPIDEMIOLOGY

- Acute myocardial infarction (AMI) is the leading cause of death in the United States
- 1.5 million events occur each year leading to 220,000 deaths
- 5% of all emergency visits are associated with chest pain
- AMI involves $150 billion for direct and indirect costs

REVIEW OF ACUTE MYOCARDIAL INFARCTION

- There are two types of AMI – STEMI and NSTEMI
  - STEMI (ST Elevated Myocardial Infarction) characteristics:
    - 100% occlusion of coronary vessel
  - NSTEMI (Non ST Elevated Myocardial Infarction) characteristics:
    - T wave inversion
    - ST depression
    - Less than 100% occlusion

PATHOPHYSIOLOGY

- Dyslipidemia
- Coronary atherosclerosis
- Plaque disruption
- Thrombosis
- Demand > Supply
SUPPLY VS. DEMAND

- Oxygen supply – factors that increase supply
  - Blood flow
  - Oxygen carrying capacity
- Oxygen demand – factors that increase demand
  - Heart rate
  - Contractility
  - Wall stress

DIAGNOSIS

- Creatine kinase myocardial band (CK-MB)
  - Shorter duration, back to normal values in 48 hours
- Troponin
  - Longer duration
  - Detectable up to 10 days after onset
- Electrocardiograms (ECG)
- Medical history
  - Symptoms – note that symptoms are atypical in female, diabetic, and elderly patients

TREATMENT

- Reperfusion depending on type and severity (TIMI score)
- Percutaneous intervention (PCI)
- Coronary artery bypass graft (CABG)
- Fibrinolysis
- Conservative Therapy
  - Morphine
  - Oxygen
  - Nitroglycerin
  - Aspirin
  - Beta-blockers (BB)/ Calcium Channel Blockers (CCB)
  - Angiotensin Converting Enzyme Inhibitor (ACEI)
  - Statins
  - Anticoagulation
  - Clopidogrel

SECONDARY PREVENTION WITH A BETA-BLOCKER

- Secondary preventions help reduce the chance for death, stroke, and recurrent infarction after an AMI event.
- There are a handful of effective secondary preventative measures, with varying levels evidence behind them, but beta-blockers provide a proven low-cost option that, in most cases, carries little risk in relation to the greatly improved patient outcomes.
  - Beta-blockers are strongly indicated in the following cases:
    - All patients recovering from AMI unless contraindicated; continued indefinitely. (Class I – Evidence Level B)
    - All patients recovering from AMI with moderate/severe left ventricular failure should receive gradual titration. (Class I – Evidence Level B)
  - It is also “reasonable” to use a beta-blocker for the following case:
    - Low-risk patients, those with normal left ventricular function, revascularized, and no high-risk features. (Class IIa – Evidence Level B)
  - The class level ranks the therapy in the given population by risk vs. benefit, with Class I being the highest level. The evidence level ranks the breadth of populations evaluated using a drug, with Evidence Level A ranking the highest.

BETA-BLOCKER BENEFITS

- Benefits of beta-blocker therapy include decreased heart rate, contractility, and blood pressure which lead to decreased oxygen demand
- Beta-blockers can also:
- Decrease the mortality rate in AMI patients by 23%\(^5\)
- Decrease the incidence of ventricular arrhythmias
- Decrease further infarction
- Decrease the chance of reinfarction by 28%\(^6\)

**Recommendations\(^1-3\)**

- Oral therapy should be initiated before discharge
  - IV formulation only for the first 48 hours with hemodynamically stable patients with persistent ischemia, hypertension, and tachycardia
  - An oral beta-blocker should be used indefinitely unless contraindicated
  - The dose may need to be titrated up to the targeted range
- No one agent is completely superior over the others, but studied agents are obviously preferred so that treatment can be matched with successful trials
- No intrinsic sympathomimetic activity (ISA) beta-blockers

**Beta-Blocker Agents\(^7\)**

<table>
<thead>
<tr>
<th>Cardioselective Beta-1-Blockers</th>
<th>Non-Selective Beta-Blockers</th>
<th>Intrinsic Sympathomimetic Activity (ISA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol (Tenormin)</td>
<td>Carvedilol (Coreg)</td>
<td>Acebutolol (Sectral)</td>
</tr>
<tr>
<td>Metoprolol tartrate (Lopressor)</td>
<td>Propranolol (Inderol)</td>
<td>Carteolol (Cartol)</td>
</tr>
<tr>
<td>Metoprolol succinate (Toprol XL)</td>
<td>Timolol (Blocadren)</td>
<td>Penbutolol (Levatol)</td>
</tr>
<tr>
<td>Betaxolol (Kerlone)</td>
<td>Labetalol (Trandate, Normodyne)</td>
<td>Pindolol (Visken)</td>
</tr>
<tr>
<td>Bisoprolol (Zebeta)</td>
<td>Nadolol (Corgard)</td>
<td>-</td>
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<tr>
<td>Nebivolol (Bystolic)</td>
<td>-</td>
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</tr>
</tbody>
</table>

Drugs appearing in bold text are FDA approved.

- Cardioselective beta-blockers only bind to Beta-1 adrenergic receptors
- Non-selective beta-blockers exhibit Beta-1, Beta-2, and/or Alpha-1 properties
- ISA beta-blockers are partial agonists
  - Agonism/antagonism depends on the concentration of the agent
  - This class of beta-blockers is not recommended for treatment of AMI or as secondary prevention of AMI

**FDA Approved Beta-Blocker Agents\(^6\)**

<table>
<thead>
<tr>
<th>Beta Blockers</th>
<th>Target Dose</th>
<th>Landmark Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol</td>
<td>100 mg twice daily</td>
<td>TIMI II-B</td>
</tr>
<tr>
<td>Atenolol</td>
<td>100 mg once daily, 50 mg twice daily</td>
<td>ISIS-1</td>
</tr>
<tr>
<td>Propranolol</td>
<td>80 mg three times daily</td>
<td>BHAT</td>
</tr>
<tr>
<td>Timolol</td>
<td>10 mg twice daily</td>
<td>Norwegian Multicenter Study Group</td>
</tr>
<tr>
<td>Carvedilol (LV dysfunction post MI)</td>
<td>25 mg twice daily</td>
<td>CAPRICORN</td>
</tr>
</tbody>
</table>

Dose should be titrated toward targeted dose if possible.
Adverse Effects

- Bradycardia
- Fatigue
- Masked signs and symptoms of hypoglycemia
- Bronchospasm
- Sexual dysfunction
- Depression

Beta-Blocker Contraindications

- Severe heart failure requiring IV diuretics and inotropes
- Low cardiac output
- Risk of cardiogenic shock
- Second/third degree heart block
- Bradycardia
  - Heart rate < 50 beats per minute
- Hypotension
  - Systolic blood pressure < 90 mmHg
- Reactive airway disease
  - Active/severe asthma

Beta-Blocker Under-Utilization

- In the past, fewer than half of AMI patients have been prescribed a beta blocker in a chronic setting. Much of this was due to concerns and/or misconceptions about the following:
  - Side effects profile
  - Lack of efficacy
  - Safety issues for those with relative contraindications
    - Heart failure
    - COPD/mild asthma
    - Diabetes mellitus
    - Intolerability in the elderly
  - These areas of concern are now better understood and altered regimens are available.

**Flowchart:**

- **HF, COPD, DM, PVD, 1° AV Block?**
  - **NO**
    - Use beta-blocker agents and do not discontinue abruptly
  - **YES**
    - **HF** – Treat w/diuretic, ACEI, monitor for weight gain
    - **COPD** – B1 selective agents (metoprolol and atenolol)
    - **Diabetes Mellitus**
    - **Peripheral Vascular Disease**
    - **1st degree Atrioventricular block**
      - Initiate low dose of beta-blocker and increase as tolerated
HEDIS Measures\textsuperscript{9,10}

- Developed by the non-profit National Committee of Quality Assurance (NCQA), the Healthcare Effectiveness Data and Information Set (HEDIS) Measures allow quantitative comparisons between health plans.
- Though design primarily for the representatives of end users of the health care products (e.g., employers), HEDIS data are also used by more than 90% of America's health plans to measure their own performance against that of their competitors.
- These measures range from performance on various aspects of comprehensive diabetes care, such as eye exams and HbA1C screening, to flu vaccination rates.
  - There are currently 71 such measures in the HEDIS data set.

**Beta-Blocker Treatment After a Heart Attack**

- In 1996, the NCQA began including discharge prescription rates for beta-blockers after an acute myocardial infarction to encourage their use.
  - From 1996 to 2006, prescription rates upon discharge rose drastically.
- By 2002, the mean beta-blocker prescription rate upon discharge among participating health plans was above 90%.
  - Because of the virtually universal increase in this measure, the NCQA introduced a second measure in 2004 that tracked persistence of beta-blocker medication use for the six month period following discharge.
  - The NCQA retired the original “Beta-blocker treatment after a heart attack” measure in 2007 and left the “Persistence of beta-blocker treatment after a heart attack” to take its place.

**Persistence of Beta-Blocker Treatment After a Heart Attack**

- HEDIS measures are calculated as fraction
- For this measure:
  - Eligible population
    - Patients 18+ years old
    - Patients 180 days post MI
    - Patients with ICD-9 code of 410.xx (for acute MI) within the measurement year
    - Exclude patients with various ICD-9 codes for contraindications
  - Numerator = the # of eligible population that was adherent
    - Adherence defined as having no aggregate gap of more than 45/180 days = 75% days covered
  - Denominator = the eligible population
- Gaps in therapy are derived from prescription claims

<table>
<thead>
<tr>
<th>Year</th>
<th>Commercial</th>
<th>Medicare</th>
<th>Medicaid</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>74.4</td>
<td>82.6</td>
<td>76.6</td>
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<tr>
<td>2008</td>
<td>75.0</td>
<td>79.7</td>
<td>73.6</td>
</tr>
<tr>
<td>2007</td>
<td>71.9</td>
<td>75.5</td>
<td>62.0</td>
</tr>
<tr>
<td>2006</td>
<td>72.5</td>
<td>69.6</td>
<td>68.1</td>
</tr>
<tr>
<td>2005</td>
<td>70.2</td>
<td>65.4</td>
<td>69.8</td>
</tr>
<tr>
<td>2004</td>
<td>67.4</td>
<td>61.3</td>
<td>69.9</td>
</tr>
</tbody>
</table>
**Beta-Blocker Long-term Adherence**

National evaluation of adherence to B-blocker therapy for 1 year after acute myocardial infarction in patients with commercial health insurance. Kramer, et. al

<table>
<thead>
<tr>
<th>Design</th>
<th>1 year, nation-wide, multi-center, double-blind, retrospective analysis</th>
</tr>
</thead>
</table>
| Goals  | • Describe long-term beta-blocker use  
• Describe temporal trends in adherence  
• Describe factors that may be associated with lower long-term adherence |
| Inclusion Criteria | • ≥ 35 years old  
• Hospitalized for AMI (ICD code 410.x1) in 2001  
• Survived for 1 year after incident |
| Exclusion Criteria | • Not continuously enrolled in health plan for ≥ 1 year after incident (death implied)  
• No prescription drug benefits  
• Inpatient or outpatient records indicate contraindications of  
• Hypotension  
• Bradycardia  
• Heart block greater than the first degree during hospitalization or 360 days after discharge |
| Primary Outcome | Adherence to a beta-blocker for 360 days after discharge for MI |
| Secondary Outcomes | • Adherence to beta-blocker for 30, 90, 180, and 270 days after discharge  
• Association of adherence over 360 days to age group, sex, health plan product (commercial or medicare/choice), and geographic region  
• Commercial = HMO, PPO, POS, and indemnity |
| Method | • Data was contributed by 11 health plans  
• All subjects were covered by prescription drug benefits to limit the effect of the cost barrier  
• Data was standardized and aggregated  
• Pharmacy claims 90 days before discharge were evaluated to capture pre-existing prescriptions  
• Pharmacy claims until 360 days after discharge were included  
• The following adherence intervals were examined:  
  • 0-30, 31-90, 91-180, 181-270, and 271-360 days after discharge  
• Any beta-blocker on the HEDIS list was acceptable  
• Changes in beta-blocker or dosage were not tracked  
• PDC = DS / DIP  
  • PDC = proportion of days covered  
  • DS = # of days of supply  
  • DIP = # of days in period  
• Adherence is defined as ≥ 75% of days covered |
| Statistical Methods | • Aggregated data – no stats were represented by weighted averages, percentages, and frequencies  
• Comparisons – compared using chi-squared test  
• Multivariable logistic regression model  
  • Age group  
  • Sex  
  • Region  
• Health plan product with 360-day adherence |
| Results | • PDC of women 35-64 < PDC of all other groups  
• Author thinks that reason most young women think that recurrent of MI is least likely to happen to them vs. older men  
• 15% absolute drop in adherence (69% to 54%)  
• From 0-30 day interval → 31-90 day interval (p < 0.001)  
• Per 2001 HEDIS measure (the year this study examined), Rx upon discharge for Medicare = 92.9%  
• This study shows that adherence rate from 0-30 day post MI was 52% for Medicare patients, so it is quite a drop |
| Author’s Conclusions | • Without the cost factor, there was still a large decline in adherence over the 360 day observation period  
• The most marked decrease in adherence was during the initial 90 day period |
| Critique | • Limitations:  
  • Aggregate data precludes researchers from analyzing adherence as continuous variable  
  • Also inhibits ability to pair clinical outcomes with individual patients to investigate the effect of adherence  
• No record of prescriptions upon discharge  
• Strengths:  
  • Research models actual care, so it is more relevant  
  • Large and diverse sample |
Adherence is a complex subject with little easily replicable evidence to be found.

In a Cochrane review of 69 randomized controlled trials, there was no clear consensus on the simplest method to improve adherence to medication regimens.12

Scott and White Quality Improvement Program

The goal is to improve the medication adherence for better outcomes for patients post MI

Beta-blockers were chosen because of their emphasis under the HEDIS measures

Applies only to the commercial plan because of legal issues with cost-interventions for Medicare

Included below is a sample survey that was administered to post-MI patients that were counted amongst the non-adherent in last year’s measure

- The intent of the survey was to find common reasons for non-adherence
- This survey was adapted from the Merck Adherence Estimator survey that has proven to be between 66-85% accurate at gauging future adherence levels

SURVEY COPY

1. How are you doing with your medications?
   Are you having any difficulty getting your prescriptions?

2. What are you taking?

3. Are you taking ____________________?
   a. If so, how are you taking this medicine?
   b. If not, why aren’t you taking this medicine?

Was the medicine stopped by your doctor? __________

Did you have side effects from the medicine? __________

Was the medicine too expensive? __________

Was the medicine changed by your doctor?

5. Where have you been obtaining this prescription?
   a) SWHP Pharmacy
   b) Samples
   c) Manufacturer
   d) Other pharmacy $4 plan
   e) Canada or Mexico
   f) Other source
   g) other insurance or pay cash?

6. To better understand your views on this medicine, please rate the following statements (agree or disagree and completely, mostly or somewhat)
   a. I worry that ___________________ will do me more harm than good.
      Agree completely Agree mostly Agree somewhat Disagree somewhat Disagree mostly Disagree completely

   b. I am convinced of the importance of ____________________.
      Agree completely Agree mostly Agree somewhat Disagree somewhat Disagree mostly Disagree completely

   c. I feel financially burdened by my out-of-pocket expenses from ____________________.
      Agree completely Agree mostly Agree somewhat Disagree somewhat Disagree mostly Disagree completely
• Survey was conducted via telephone
• 66 patients were called and 11 were available to take the survey
• Results:
  o Lack of knowledge
    ▪ Most thought the beta-blocker was for hypertension
    ▪ Some had no idea of its indication
  o Lack of commitment
    ▪ No refills, no re-evaluation requested from primary care physician
  o Cost issues
    ▪ 30% fill with an outside pharmacy that has a $4 list of generic medications.

**IMPROVING ADHERENCE**

• Merck Adherence Estimator\(^3\)
  o Identifies reasons for non adherence
    ▪ Education
    ▪ Behavior/commitment
    ▪ Cost
  o Predicts future adherence issues

**INTERVENTIONS**

• Knowledge
  o Send out educational material regarding the importance of the beta-blocker therapy
    ▪ Emphasize its effect in the prevention of further cardiovascular events
  o Possible counseling session before discharge by clinical pharmacists
  o Encourage more counseling in the outpatient setting, including phone calls

• Behavioral
  o Mail order pharmacy to provide convenience
  o Phone call reminders assessing whether they have followed-up with their PCP after discharge

• Cost
  o Waive co-pay for all beta blockers for post-MI for at least six months
**Adherence Reasons and Interventions**

<table>
<thead>
<tr>
<th>Randomized Trial of Direct-to-Patient Communication to Enhance Adherence to B-Blocker Therapy Following Myocardial Infarction. Smith, et. al.¹⁰</th>
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<tbody>
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<td><strong>Design</strong></td>
</tr>
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</tr>
<tr>
<td><strong>Method</strong></td>
</tr>
<tr>
<td><strong>Statistical Methods</strong></td>
</tr>
<tr>
<td><strong>Results</strong></td>
</tr>
<tr>
<td><strong>Author’s Conclusions</strong></td>
</tr>
<tr>
<td><strong>Critique</strong></td>
</tr>
<tr>
<td><strong>Strengths:</strong></td>
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<tr>
<td>Predictors of Early Discontinuation of Evidence-Based Medicine After Acute Coronary Syndrome. C. Melloni, et al19</td>
</tr>
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</tr>
<tr>
<td><strong>Design</strong></td>
</tr>
</tbody>
</table>
| **Goal** | To identify reasons of low adherence  
Investigate the role of the provider in early evidence-based medicine (EBM)  
Describe factors associated with self-discontinuation in patients |
| **Inclusion Criteria** | CRUSADE and ACTION  
Acute ischemic symptoms at rest lasting ≥ 10 minutes within 24 hours of hospitalization  
≥ 1 high risk feature (ST segment changes and/or positive cardiac markers) |
| **Exclusion Criteria** | Death during hospitalization  
Incomplete 3 months follow-up  
Too ill, deaf, refused, died, language barrier  
Medications marked as not prescribed  
Undetermined persistence |
| **Primary Outcome** | Determine the persistence use of selected medication classes 3 months after a hospital discharge |
| **Method** | 3 month follow-up rate of 93.5%  
Medications were sorted by class  
Antplatelets (ASA/clopidogrel)  
Beta Blockers  
Angiotension Converting Enzyme Inhibitors / Angiotensin Receptor Blockers  
Lipid Lowering (Statins and Non-Statins)  
Telephone call on a 3 month follow-up, patients self-reported on medication use  
This was compared with the prescribed regimen upon discharge  
Patients were designated persistent if they were still taking the same class of medication  
Separated to three groups:  
- EBM persistent  
- EBM discontinued with provider input  
- EBM self-discontinued |
| **Statistical Methods** | Compared each of the following to each persistence designation:  
Baseline characteristics  
Socioeconomic data  
Behavior data  
Patient-provider communication  
Financial burden  
Secondary prevention  
Use of medication ingestion reminders  
Continuous variables were analyzed using the Pearson chi-square test  
Categorical variables were analyzed using the Kruskal-Wallis test  
Factors associated with respective persistence categories were evaluated in a multivariate model |
| **Results** | No significant differences in baseline characteristics between patients who self-discontinued and persistence or discontinued by provider  
Factors that positively affected adherence (p > 0.05):  
- Having health benefits  
- Using a pill-box, calendar, or alarm  
- Having a diet/exercise program  
- Making an appointment with a cardiologist |
| **Author’s Conclusions** | Costs, patient education, and reminder methods can play an important part in the adherence of a patient |
| **Critique** | Limitations:  
- Self-reported medication adherence and provider involvement  
- Measures short-term adherence (3 months), which may not reflect long term predictors of adherence  
Strengths:  
- Unique in that it is able to quantify self-discontinuation vs provider-sanctioned discontinuation |
**CONCLUSION**

- Patient education is an important factor in helping patients to stay adherent to their medications.
- Cost may not be the primary reason of non adherence, but it can still contribute.
- A prescription for a beta-blocker upon discharge is not enough of an intervention to assure long term persistence.
- Adherence is a difficult concept to quantify accurately and may never be fully understood.
- Both inpatient and outpatient care play a huge role in patient survival after an acute MI.
- The impact can be influenced by our diligence in helping patients adhere to their treatment.
- Our best tool is patient counseling.
- Every time a beta blocker is filled, let’s not assume that it is for hypertension!!!

**REFERENCES**


