Worksheet No. ACS-023A.doc  Page 1 of 25

WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care
Worksheet author(s)

| Worksheet Author: Dawn Yin Lim | Date Submitted for review: August 12, 2009 |

Clinical question.

**Question:** "In patients with suspected ACS/MI in prehospital and emergency department settings (P), does the use of beta-blockers (I), compared with standard management (ie. no prehospital and emergency department use of beta-blockers) (C), improve outcome (eg. arrhythmias, infarct size, ECG resolution, survival to discharge, 30/60 d mortality) (O)?"

**Is this question addressing an intervention/therapy, prognosis or diagnosis?** Intervention/Therapy

**State if this is a proposed new topic or revision of existing worksheet:** Revision of existing worksheet (ILCOR 2005)

Conflict of interest specific to this question

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

Search strategy (including electronic databases searched).

**Database: Ovid MEDLINE(R) <1950 to August Week 2>**
**Search Strategy:**

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<td>6 and 15</td>
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</table>

**Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <August 11, 2009>**
**Search Strategy:**

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<th>Results</th>
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<tr>
<td>1</td>
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3 1 and 2
4 limit 4 to yr="1983 - 2009" 46

Database: All EBM Reviews - Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, and NHSEED (August 11, 2009)

Search Strategy:

Database: EMBASE <1980 to 2009 Week 32>

Search Strategy:

AHA EndNote Master library (March 24, 2008 Edition)

State inclusion and exclusion criteria

Inclusion:
1. Pre-hospital or emergency department use of beta blockers given within 24 hours of symptom onset
2. Described and evaluated the use of beta blockers in the study
3. Targeted patients who were suspected of experiencing an acute coronary syndrome
Exclusion:
1. Animal studies
2. Papers before 1983 (since the 2005 ILCOR worksheet has taken into consideration available literature since the 1960s)

• Number of articles/sources meeting criteria for further review:

48 papers were identified for further review. Papers were excluded because they were: editorials or guidelines based on original studies.
31 papers were included in the final analysis (3 meta-analysis/systematic reviews, 20 RCTs, and 8 retrospective analyses of RCTs).

Summary of Evidence

Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Good</th>
<th>Evidence Supporting Clinical Question</th>
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<tbody>
<tr>
<td>*COMMIT</td>
<td>*Hjalmanson et al., 1983 (Goteborg Trial)</td>
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<tr>
<td>Collaborative</td>
<td>E1, E4, E5 (but no p-value provided for A and the support for F was data derived)</td>
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<tr>
<td>Group, 2005</td>
<td>Malmberg, K., J. Herlitz, A. Hjalmanson et al., 1989 E4</td>
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<tr>
<td>(increases cardiogenic shock)</td>
<td>(Retrospective on Goteborg and MIAMI Trials)</td>
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<tr>
<td>*ISIS-1 (First International Study of Infarct Survival) Collaborative Group, 1986 E4</td>
<td>Herlitz, J., F. Waagstein et al., 1997 E4</td>
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<tr>
<td>(mainly see early improvement in mortality)</td>
<td></td>
</tr>
<tr>
<td>Level of evidence</td>
<td>A = Return of Spontaneous Circulation</td>
</tr>
<tr>
<td>-------------------</td>
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<tr>
<td>Good</td>
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* Indicates Key Study
<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>E1, E2, E4</th>
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<tr>
<td>Basu, Senior et al. 1997</td>
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<tr>
<td>Murray, DP., RG. Murray et al., 1988</td>
<td>E2</td>
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<td>Al-Reesi, A., N. Al-Zadjali et al., 2008</td>
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<td>Heidbuchel, JT., J. Tack et al, 1994</td>
<td>E1</td>
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<td>Yusuf, Peto et al. 1985</td>
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<tr>
<td>Freemantle, Cleland et al., 1999</td>
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<tr>
<td><strong>Fair</strong></td>
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<tr>
<td>Salathia et al. (1985)</td>
<td>E4</td>
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<tr>
<td>Owensby, DA, 1985</td>
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<tr>
<td>Rehnqvist, Olsson et al., 1987</td>
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<tr>
<td><strong>Poor</strong></td>
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<tr>
<td>Di Pasquale, Paterna et al., 1994</td>
<td>E1, E2, E4</td>
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<tr>
<td>Alberque, 1994</td>
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<tr>
<td>Brown, MA., RM Norris et al., 1985</td>
<td>E2</td>
</tr>
<tr>
<td>Coletta, C., R. Ricci et al., 1999</td>
<td>E4, E5</td>
</tr>
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</table>

**Level of Evidence**

A = Return of Spontaneous Circulation
B = Survival of Event
C = Survival to Hospital Discharge
D = Intact Neurological Survival
E1 = Prevent Arrhythmias
E2 = Decrease Infarct Size
E3 = Improve ECG Resolution
E4 = Improve 30/60 Day Mortality
E5 = Prevent Re-infarction
E6 = Increase Incidence of Congestive Heart Failure
E7 = Decrease mechanical rupture
E8 = Increase cardiogenic shock
E9 = Miscellaneous Side Effects

* Indicates Key Study

### Evidence Opposing Clinical Question

<table>
<thead>
<tr>
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</table>

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E9 = Miscellaneous Side Effects

* Indicates Key Study

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**REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:**

**Limitations of this Worksheet:**

This worksheet did not look at coronary syndromes precipitated by toxicologic phenomena (i.e. cocaine). Also, this worksheet focused on investigating beta-blocker use for the treatment of suspected acute STEMI and NSTEMI (and not for unstable angina, although UAP is included in the spectrum of ACS).

**Challenges to Answering this Worksheet Question:**

There were a few challenges with assessing beta-blocker administration in the context of suspected ACS/MI from the pre-hospital and emergency department settings, namely:

a) There is a dearth of studies investigating the administration of beta-blockers in the pre-hospital setting.

b) There is a dearth of studies investigating the administration of beta-blockers in the setting of primary percutaneous intervention, and (though to a lesser extent) in the era of thrombolytics. In the citation list, the designation of trials as pre-thrombolytic, post-thrombolytic, and PCI/angioplasty trials is clearly listed. No designation was given for review papers.
c) The time windows within which beta-blockers were administered in suspected ACS/MI varied considerably from study to study. Therefore, it was not always clear whether the intervention of beta-blocker treatment had occurred in the emergency department or in the CCU much later (but still within the acceptance window). In the citation list, the time window within which beta-blockers were administered is highlighted in bold print.

There have been many studies over the years regarding the value of administering beta-blockers in the setting of suspected acute ACS/MI. Many studies have shown a clear benefit in the areas of mortality reduction, decreased infarct size, prevention of arrhythmias, prevention of mechanical complications, and prevention of re-infarction. However, many of the early beta-blocker trials were small and had wide confidence intervals. Many studies have also shown no particular benefit in these areas. Of note, none of the papers reviewed showed that beta-blockers caused irreversible harm.

There are very few studies in the current literature that study the effects of beta-blocker in conjunction with the practice of primary percutaneous coronary intervention. Although several large beta blocker trials in the early 1980s showed generally favourable effects by starting intravenous then oral beta blocker therapy in the early hours after a suspected acute coronary syndrome, the studies were made before the advent of medical and mechanical reperfusion strategies that have since become the standard of care. More trials (like COMMIT) studying beta-blocker usage in the setting of current standard management protocol for ACS/MI would help answer this study question more definitively.

Since it is difficult to determine what time frame coincides with any given patient’s stay in the emergency department before hospital admission (for instance, in centres with primary PCI a patient may spend only minutes in the emergency department while a patient may be in the emergency department for hours before admission to a CCU in other centres without CODE STEMI protocols), it makes more sense to focus on the number of hours post symptom onset within which administration of beta-blockers will show the greatest benefit or harm. Since several of the studies did not describe in detail the exact times that corresponded to “early” treatment (i.e. many studies accepted patients and administered treatment medications “as soon as possible” but did not distinguish if patients actually received treatment < 2 hours or < 4 hours etc.), it is possible that there may be patterns of benefit or harm that we cannot extract easily from the current literature.

Preface:

All trials had relatively similar exclusion criteria for administration of beta-blockers. These criteria include (but are not necessarily limited to): moderate to severe congestive heart failure, hypotension, bradycardia, heart block, and reactive airway disease.

**EMERGENCY DEPARTMENT ADMINISTRATION OF BETA-BLOCKERS:**

**Prevention of Arrhythmias:**

The occurrence of ventricular fibrillation (VF) was clinically and statistically decreased in several trials (COMMIT 2005, Hjalmarson 1983, Jurgensen 1984, Herlitz 1984, Herlitz 1988). One trial also demonstrated a clinically significant decrease in ventricular tachycardia (VT) requiring treatment. This finding approached statistical significance (Herlitz, Edvardsson et al. 1984).

Supraventricular dysrhythmias, including atrial fibrillation and atrial flutter, occur with less frequency in AMI patients treated with iv beta-blockers (Herlitz, Edvardsson et al. 1984, MIAMI 1985).

However, other studies (including large multi-centre randomized controlled trials), did not demonstrate a modulation in ventricular dysrhythmias in patients with AMI treated with iv beta-blockers (MIAMI 1985, ISIS-1 1986, Rehnqvist, Olsson et al. 1987, Heidbuchel 1994). The use of beta-blockers demonstrated a trend in one trial towards reduction in ventricular dysrhythmias, yet this did not achieve statistical significance (Pfisterer, Cox et al. 1998).

**Infarct Size:**

Many studies attempted to answer whether acute beta-blockade post ACS/MI decreased infarct size. Over the years, different methods have been used to correlate with infarct size (for e.g., levels of SGOT, LDH, CK, QRS vector parameters, echocardiographic volume measurements). Many trials have shown that rough correlates of infarct size were decreased with early iv beta-blocker administration (International Collaborative Study Group 1984, Jurgensen 1984, Gupta 1985, Risenfors 1991, and Herlitz 1988) including a trial done in the PCI era (Galcera-Tomas 2001).

A few well designed studies showed no apparent effect on infarct size correlates with early iv beta-blocker treatment (MIAMI 1985 and Murray 1988).

**ECG Resolution:**

This aspect was largely addressed in trials looking at the effect of acute administration of beta-blockers on infarct size (see above).

**Survival to Discharge:**

This aspect was largely addressed in trials looking at mortality and is easier to discuss in that section since the observation period for mortality varied so widely from one trial to another.

**Mortality:**
There was a wide variation in the time period to which mortality was measured post MI. Some trials measured mortality at as little as 7 days post-infarction while others extended their period of observation to a year and beyond.

In patients with acute myocardial infarction (AMI), intravenous (iv) beta-blockers were shown to reduce mortality in the acute treatment period (Hjalmarson “Goteborg Trial” 1983, ISIS-1 1986, Herlitz 1988, Herlitz 1997, Pfisterer 1998, and Piccini 2008). This mortality benefit was maintained at one-year follow-up (Hjalmarson 1983 and ISIS-1 1986). In particular, a retrospective analysis of the Goteborg trial suggested that earlier administration of beta-blocker < 8 hours after symptom onset had an even more significant effect on mortality reduction (Herlitz 1988). In one retrospective analysis of the Goteborg and MIAMI trials, patients with diabetes seemed to experience an even greater reduction in mortality than their non-diabetic counterparts (Malmberg 1989).

In a meta-analysis of ISIS-1 + MIAMI + 26 smaller beta-blocker trials, the incidence in the first seven days of death, re-infarction, and ventricular fibrillation (VF) was significantly lower in patients with AMI treated with iv beta-blockers (ISIS-1 1986 extended analysis).

However, two key beta-blocker studies including over 51,000 patients showed no effect on mortality by using beta-blockers acutely (MIAMI 1985 and COMMIT 2005). These studies allowed patients to be enrolled up to 24 hours post symptom onset which made it difficult to determine how early the beta-blockers were administered. In MIAMI, only 25% of the patients were enrolled within 4 hours while the rest of the patients were enrolled within 12 hours. The COMMIT trial was not so explicit about the timing of beta-blocker administration.

Furthermore, one meta-analysis of early iv beta-blocker administration (which preceded ISIS-1) failed to demonstrate this mortality reduction. The administration of early oral beta-blockers also did not alter one-week mortality (Yusuf, Peto et al. 1985). These neutral findings were supported by a second meta-analysis performed on similar trials accepting patients treated up to 72 hours post onset of symptoms (Al-Reesi 2008). Interestingly, this study did note a significant reduction in mortality in their subgroup of low risk (Killip Class I) patients. One systematic review showed no advantage of acute iv beta-blockers on mortality at 6 weeks (Freemantle 1999).

Three trials showed no difference in acute or long term mortality with early iv beta-blocker administration in the setting of fibrinolysis (Roberts, Rogers et al. 1991, Di Pasquale 1994, COMMIT 2005). One large trial did show a decrease in 30 day mortality if either iv or oral beta-blocker was given acutely, but this decrease in mortality was lost when iv + oral was compared to oral administration alone (Pfisterer, Cox et al. 1998).

One post-hoc analysis demonstrated improved 30 day mortality in patients receiving iv beta-blockers prior to PCI. This net benefit resulted exclusively from the mortality reduction in patients who had not previously been on oral beta-blockers prior to hospital admission. There was no reduction in thirty day re-infarction (Halkin, Grines et al. 2004).

Re-infarction:

Two large well designed studies suggested that treatment with acute iv beta-blockers decreased the incidence of re-infarction (COMMIT 2005, Hjalmarson 1983) although the observation in the Goteborg trial was data derived. In patients treated with a fibrinolytic for AMI, concomitant use of iv beta-blockers reduced the risk of non-fatal re-infarction during the acute treatment period. This effect was not preserved at long term follow-up once treatment was discontinued (Roberts, Rogers et al. 1991, Basu, Senior et al. 1997).

Miscellaneous Side Effects:

The use of early oral or iv beta-blockers in all patients with presumed AMI did not increase the risk of developing congestive heart failure (CHF), hypotension or heart block in one large meta-analysis pooling the data from all iv beta-blocker trials (both given acutely and long term) until the mid-1980s (Yusuf, Peto et al. 1985). In patients with mild to moderate CHF, iv beta-blockers reduced three month and one year mortality. There was no significant increase in treatment side effects within this subgroup (Herlitz 1997).

One study (Halkin, Grines et al. 2004) noted an increased incidence of CHF in the patients treated with beta-blockers acutely. IV beta-blockers, when compared with oral beta-blockers administered in the first 24 hours, had an increased incidence of both CHF and cardiogenic shock. The clinical implications are important, but difficult to generalize owing to the post-hoc study design and imprecise definition of CHF (Pfisterer, Cox et al. 1998). Increased cardiogenic shock was also seen in the COMMIT 2005 trial.

In ISIS-1, the greatest benefit in mortality occurred on days 0-1. The highest use of inotropes in the treatment arm occurred in this same time period (presumably to counteract the resulting hypotension and shock post beta blockade). This finding seems to suggest that although the rate of hypotension and shock may be increased in the acute setting post beta-blockade, it was a reversible side effect that did not result in an increase in mortality. However, this observation from the authors was not followed by a detailed analysis of whether the patients experiencing hypotension and cardiogenic shock secondary to iv beta-blocker administration were the same ones who were also treated successfully with inotropes.

Mechanical complications of AMI, specifically cardiac rupture, were reduced in patients treated with iv beta-blockers (ISIS-1 1988). The incidence of cardiac tamponade was decreased in patients treated with iv beta-blockers. However, this finding was paired by a similar reduction in cardiac tamponade among patients treated with only oral beta-blockers (Pfisterer, Cox et al. 1998).
There is too little data to support extrapolating beta-blocker usage in the pre-hospital time period for suspected ACS/MI. One study did include a pre-hospital component of beta-blocker administration which overall showed decreased infarct size correlates in patients treated with iv beta-blockers (Risenfors, M., J. Herlitz et al, 1991) but the data to support or go against the administration of beta-blockers in suspected ACS/MI is still lacking.

Acknowledgements: Dr. Jon Sherbino, Dr. Gilson Feitosa Filho

Citation List

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B = Survival of Event  
C = Survival to Hospital Discharge  
D = Intact Neurological Survival  
E1 = Prevent Arrhythmias  
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* Indicates Key Study

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Citation Summary</th>
</tr>
</thead>
</table>

1. Yes, treatment was “randomized” but in a very bizarre fashion. Pre-hospital workers would treat with either atenolol or placebo and then the treating doctor in the hospital would decide whether to continue with the treatment medication in the medication kit (which was arranged to avoid “beta blocker” overdose"
2. There is no mention of randomization lists. However, the centres involved in the study received numbered treatment boxes with the study medications.
3. All subjects were accounted for at the end but many did not receive any of the hospital treatment
4. As soon as a treatment box was open, the patient was considered to be included in the study regardless of receiving any medication (i.e. analyzing with intention to treat)
5. Yes, this is touted as a double blinded study
6. Yes, other than the experimental treatment the patients were treated equally
7. Yes, the groups were similar at the end of the trial

Study Details:
- Design: Double-blind RCT
- N = 77
- Intervention: In the pre-hospital setting, if EMS noticed signs and symptoms of AMI < 2 hrs after symptom onset, they would initiate take down details of the patient and enter them into the study
- Treatment arm included atenolol 5 mg x 2 iv then a 50 mg po tablet placebo treatment to be made at the discretion of the ED doctor (to avoid “beta blocker overdose” whereas the placebo arm included placebo iv injections immediately followed by a 50 mg po atenolol tablet to be used at the discretion of the ED doctor; in hospital, all patients openly received atenolol 100mg po x 7 days

Results:
- Delay to treatment: 182 min ED vs 94 min pre-hospital
- 50 patients withdrew from treatment protocols
- Death 3/36 control arm vs 3/41 treatment arm

Evidence: Poor study, LOE 1, Neutral (Criteria E4)
<table>
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<tbody>
<tr>
<td><strong>Meta-analysis</strong></td>
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1. Specific objectives of the review: to determine whether patients receiving beta blockers within 72 hours post MI reduced mortality rate at 6 weeks  
2. Yes, the study design was defined.  
3. Yes, inclusion and exclusion criteria were stated.  
4. The paper omitted non-English papers and non-RCT studies.  
5. Yes, study characteristics and quality were identified.  
6. Selection criteria were applied but excluded studies were not reported? |
| **Study Design:** |  
- Design: Meta-analysis  
- N = 18 RCTs (N = 13 were high quality studies); 92% of patients in the meta-analysis were from COMMIT, ISIS-1, and MIAMI (reviewed elsewhere in this citation list)  
- Intervention: beta blocker use (oral or iv) within 72 hours |
| **Results:** |  
- Primary endpoint: mortality at 6 weeks: 74,643 patients with 5095 deaths, non-significant, OR 0.95, 95% CI 0.90-1.01  
- Subgroup analysis: statistically significant short term benefit in low risk (Killip Class I) patients: OR 0.93, 95% CI 0.88-0.99 |
| **Evidence:** | Good study, LOE1, Neutral (Criteria E4, but some benefit noted for low risk patients) |

<table>
<thead>
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<tbody>
<tr>
<td><strong>POST-Thrombolytic Trial</strong></td>
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</table>
1. Yes, patient treatment was randomized.  
2. There is no mention of concealing randomization lists.  
3. Yes, all patients were assessed after discharge from the hospital at days 14, 42, 84, and 168. But only those with confirmed myocardial infarction and who had been given at least one dose of medication were included in the analysis after randomization (whether they stayed on for the whole study or not).  
4. If patients were found to not meet the criteria of an MI, they were withdrawn from the study (even after being randomized). Otherwise, the investigators used intention to treat to analyze their subjects.  
5. Yes, the study is double blinded.  
6. Yes, both groups were treated equally.  
7. Both groups were similar at the start of the trial. |
| **Study Details:** |  
- Design: Single-centre, double-blinded, randomized, parallel-group, placebo-controlled study with stratification for location of infarction (anterior or inferior) and thrombolysis or no thrombolysis (thrombolysis was given on the treating doctor’s discretion)  
- N = 151 consecutive patients (74 placebo and 77 treatment arm) and 146 subsequently analyzed on an intention to treat basis (2 from each group did not have confirmed MI and the 1 patient had renal failure precluding the start of study medication)  
- Intervention: Carvedilol 2.5 mg IV over 15 minutes within 24 hours of onset of chest pain, then ultimately titrated to 12.5-25 mg PO BID x 6 months or until an endpoint had been reached (namely, any one of cardiac death, reinfarction, unstable angina, heart failure, emergency revascularization, ventricular arrhythmia requiring intervention, stroke, and additional cardiovascular therapy other than sublingual nitrates for angina, diuretics for hypertension, or continuation of preexisting ACE inhibitors, digitalis, or anti-arrhythmics) |
| **Results:** |  
- Primary endpoints: cardiac events (death, VF, emergent CABG, heart failure etc): 31/74 control arm vs 18/77 treatment arm, p<0.02  
- Death or re-infarction: 11/74 control arm vs 6/77 treatment arm, p = 0.12  
- 54 pts initially in acute CHF (no worsening of CHF symptoms/medication use in either group) |
| **Evidence:** | Good study, LOE 1, Neutral (Criteria C, E5, E6—but these are all grouped under “cardiac events” in the study) |
Brown, MA., RM Norris et al., 1985

**PRE-Thrombolytic Trial**


1. Yes, patients were randomized to treatment groups.
2. There was no mention of randomization lists or procedures.
3. Yes, all patients were accounted for at the end of the trial.
4. There is no mention about intention to treat.
5. There is no mention of whether the experiment was blinded.
6. Yes, both groups were treated equally.
7. The groups were different (the treatment group was older, p = 0.004)

**Study Details:**
- Design: Unblinded RCT
- N = 79 (35 in control arm, 44 in treatment arm)
- Intervention: Propanolol 0.1 mg/kg IV followed by Propanolol 320 mg po in 40 mg doses over the next 72 hours within 4 hours onset of symptoms

**Results:**
- Left ventricular function: non-significant
- Exercise capacity: non-significant

N.B. Authors suggest that this study supports data that beta blockade limits infarct size by preserving subepicardidal myocardium.

**Evidence:** Poor Study, LOE1, Neutral (Criteria E2)

Coletta, C., R. Ricci et al., 1999

**No Thrombolysis**


**Study Details:**
- Design: Unblinded RCT
- N = 236
- Intervention: po captopril titrated up to 25mg TID v. PO metoprolol titrated up to 100 mg BID v. combination
- Enrollment within 24 hrs

**Results:**
- At 6 months there was no difference in cardiac death, reinfarction, UA, CHF
- no difference in SFx

**Evidence:** Poor Study, LOE1, Neutral (Criteria E4, E5)

*COMMIT Collaborative Group

**Post-Thrombolytic Trial**


**COMMIT Trial**
1. The patients’ treatment was randomized using sequentially and pre-numbered treatment/placebo packs prepared centrally. Each pack contained the initial treatment of IV metoprolol or placebo and enough oral metoprolol for 4 weeks afterward or until discharge (as well as +/- clopidogrel). It is not clear how the packs were distributed to the hospitals and how they were randomized. As long as the treating physician believed there were no clear contraindications or indications for either metoprolol or clopidogrel (N.B. this means patients who had clear contraindications for beta blocker or who went for primary PCI—b/c clopidogrel is routinely given-- were excluded from this study), they were included in the study up to 24 hours from symptom onset. If a physician thought the patient was eligible, he would need to take the next box from the group pack and make a record of that before the patient could be entered.
2. No comment on the randomization list
3. Two patients (one in each of the treatment and placebo groups) was lost to follow up
4. The investigators used intention to treat in their analysis (e.g. even if the patient felt too unwell to continue or if the patient was eventually discovered not to have an ACS, they were evaluated with respect to intention to treat)
5. It is touted as a randomized control trial with no specific claim to blinding. The patients and clinicians who administered the drugs were “blinded” however it is likely that a clinician could certainly guess that he was giving metoprolol rather than placebo if he sees the clinical effects occur after administering the first IV dose. There is no comment on whether the investigators were blinded when evaluating the results.
6. This was a 2x2 factorial study design studying administration of metoprolol and clopidogrel, ie. A quarter of the
patients received metoprolol and clopidogrel, one quarter received only metoprolol, one quarter received only clopidogrel, and one quarter received no study drugs. The investigators justified this study design by assuming that there should be no interaction between metoprolol and clopidogrel. Also, they could answer two questions with one large study as well as see if there are any synergistic effects with the two drugs combined. The physicians were asked not to use non-study beta blocker (unless it was really indicated) during this study. Table 1 shows that the beta blocker group received less beta blocker and calcium channel blockers than the placebo arm. Other than that, the treatment of patients was subject to the treating facility i.e. the study included a heterogenous group of patients who (other than the study treatments) were treated according to the primary treating physician’s discretion.

Table 1 is like a mirror image—both arms were similar (except for the use of non-study drugs as indicated in question #6)

**Study Details:**
-N = 45852 (sufficiently powered study) at 1250 hospitals (one in each arm lost to followup)
-Intervention: placebo vs. metoprolol within 24 hours of suspected ACS (5 mg IV initially, then q2-3 minutes x 2 if patient could tolerate it) switched to 50 mg oral metoprolol q6 hrs for days 0-1, and then 200 mg po controlled release from day 2 onwards

**Results:**
-Coprimary outcomes: a) composite of death/re-infarction/cardiac arrest, and b) death from all causes during study period (up to death or day 28th)
-For death/re-infarction/cardiac arrest, 9.4% of the metoprolol arm had at least one event vs. 9.9% of placebo arm (OR 0.96, 95% CI 0.9-1.0, p = 0.1)
-For death from all causes, 7.7% in the metoprolol arm vs. 7.8% in the treatment arm (OR 0.99, 95% CI 0.92-1.05, p = 0.69)
-Retrospective analysis (broken down into many factors and shock severity): early metoprolol decreases risk of reinfarction and ventricular fibrillation but increases risk of cardiogenic shock—all secondary endpoints were significant
-Bottom line: cannot give to all patients, but may be useful if given early to a subgroup of patients presenting with ACS

**Evidence:** Good study, LOE 1, supportive in some aspects of the study question but may increase risk of cardiogenic shock, Criteria E1, E5, E8

---

**Di Pasquale, Paterna et al., 1994**

*POST-Thrombolytic Trial*


1. Yes, patients were randomized to four treatment groups (see below)
2. There is no mention of randomization lists.
3. All patients were accounted for at the end of the trial (followed until they died)
4. There is no specific mention of “intention to treat”.
5. It was a single blinded study.
6. All groups were given “standard” treatment for MI at the test centre.
7. There were fewer women included in the trial (31 F and 135 M). Other than age and baseline CK levels (which were similar) there is not other demographic data presented

**Results:**
-Design: single blind RCT
-N = 166
-Intervention:
  Four groups:
  Group A (N = 42): captopril 6.25 mg po 15 min prior to thrombolysis + metoprolol 5 mg IV x 3 within 1 hour of thrombolysis, then po metoprolol afterwards
  Group B (N = 42): captopril 6.25 mg po 15 min prior to thrombolysis (no metoprolol)
  Group C (N = 37): metoprolol 5 mg IV x 3 then orally afterwards (+ captopril started on day 3)
  Group D (N = 45): thrombolysis only (+ captopril started on day 3)
-Enrollment within 4 hrs

**Results:**
-Followup consisted of visits q3months after discharge for the first year, and then q6 months after that
-CK (U/l): Non-significant between placebo and metoprolol group
-Mortality: Non-significant
-Late ventricular arrhythmias: Non-significant

**Evidence:** Poor study, LOE1, Neutral (Criteria E1, E2, E4)
<table>
<thead>
<tr>
<th>Study</th>
<th>Title</th>
<th>Authors</th>
<th>Sample Size</th>
<th>Results</th>
<th>Evidence</th>
</tr>
</thead>
</table>
| Freemantle, Cleland et al., 1999  
  - OR 0.96 (95% CI 0.85 - 1.08) = non-significant reduction of death (NNT 250)  
  - Long term treatment (mortality at 2 yrs)  
  - OR 0.77 (95% CI 0.69-0.85); NNT = 84 (must treat for one year)  
- Initial dose given IV OR 0.87 (95%CI 0.67-1.22); no risk or benefit to giving first dose IV  
- Cardiodeselectivity OR 1.10 (95% CI 0.89 - 1.39); trend towards reduced survival  
- Intrinsic sympathomimetics activity OR 1.19 (95%CI 0.96 - 1.47); trend towards reduced survival | Good study, LOE1, Neutral (Criteria E4) |
| Galcera-Tomas, Castillo-Soria et al., 2001  
  - 29.8 +/- 12% control arm vs 20.8 +/- 12% treatment arm, (p < 0.01) by polar map and 28.3 +/- 13% vs 20.0 +/- 13% (P <0.01) by tomography | Good study, LOE1, Supportive (Criteria E2) |
| Gupta, 1985  
<table>
<thead>
<tr>
<th>Study Details:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design:</strong> randomized trial, unclear if blinding involved</td>
</tr>
<tr>
<td><strong>N = 75</strong> (25 each in the propranolol group, verapamil group, and control group)</td>
</tr>
<tr>
<td><strong>Intervention:</strong> in patients with established acute anterior MI only (all other types of MI were excluded) patients were given either: routine treatment (group I), propranolol 20 mg po QID x 21 days (group II), or verapamil 40 mg po QID x 21 days (group III) <strong>within 8 hours of symptom onset</strong></td>
</tr>
</tbody>
</table>

**Results:**
- Mean ST segment elevation: the group treated with propranolol showed a statistically significant decrease in ST segment on days 3 (p value not legible), 5 (P < 0.01) and 10 (p < 0.05)
- SGOT values: Mean values for group treated with propranolol peaked earlier than the control group

**Evidence:** Fair study, LOE1, Supportive (Criteria E2)

| Halkin, Grines et al. 2004  
*Angioplasty Trial* |
|---------------------|

1. Yes, comparison groups were clearly defined.
2. It’s unclear if there was blinding involved.
3. There is no mention of confounders.
4. Yes, follow-up was sufficient

**Study Details:**
- **Design:** post-hoc sub group analysis RCT of CADILLAC trial
- **N = 2082** (946 were not given beta blockers and 1136 were given beta blockers prior to thrombolysis)
- **Intervention:** metoprolol 5 mg iv over 2 min x 3 prior to intervention recommended as standard therapy (enrollment **within 12 h** from symptom onset)
- Patients were randomized to stent or balloon angioplasty; +/- abciximab (CADILLAC trial)

**Results:**
- **Primary endpoint:** 30 day mortality
  - All: 1.5% in beta blocker group vs. no 2.8% in no beta blocker group, p = 0.03
  - Subset of patients without prior beta blockers: 1.2% beta blockers vs. 2.9% no beta blockers, p = 0.007
  - Subset of patients with prior beta blocker treatment: 3.3% beta blockers vs. 1.9% no beta blockers, p = 0.47
- 30 day re-infarction, non-significant
- CHF: 1.1% in beta blocker group vs 0.3% in non beta blocker group; p = 0.05

**Evidence:** Fair study, LOE3, Supportive (Criteria E4, E6)

| Heidbuchel, JT., J. Tack et al, 1994  
*POST-Thrombolytic Trial* |
|--------------------------|

1. Yes, patients were randomized to treatment groups.
2. Yes, the randomization was concealed using a “double dummy” system.
3. No, not all patients were accounted for at the end of the trial (17 each in the treatment arm and the placebo arm).
4. It is not explicitly stated whether the authors used intention to treat.
5. Yes, patients and clinicians were blinded.
6. Yes, other than the treatment the groups were treated equally.
7. Yes, the groups were similar at the beginning of the trial.

**Study Details:**
- **Design:** Double blinded RCT
- **N = 244** (77 placebo, 83 atenolol, 84 alinidine)
- **Intervention:** atenolol 5 mg iv over 10 min x 2 followed by atenolol 25-50 mg po bid
- **Intervention done within 5 hours of symptom onset**

**Results:**
- **Primary endpoint:**
  - First day arrhythmias: non-significant (as determined by 24 hour Holter)
<table>
<thead>
<tr>
<th>Evidence:</th>
<th>Good study, LOE 1, Neutral (Criteria E1)</th>
</tr>
</thead>
</table>
| **Herlitz, J., N. Edvardsson et al., 1984**  
**PRE-Thrombolytic Trial**  
**Study Details:**  
- Design: Double-blind RCT  
- N = 1395  
- Intervention: metoprolol 15 mg IV (within 12 hrs), then 200mg po od x 90 days  
**Results:**  
- VF: 17 (2.4%) control v 6 (0.2%) Rx p=0.035  
- Treated VT: 26 (3.7%) control vs 14 (2.0%) treatment arm, p = 0.076  
- SVT: 0-18 h (N = 852)  
  - 75 (17.7%) control vs 42 (9.8%) treatment, p <0.001  
  - 18h - 4 d (N = 930)  
  - 88 (18.9%) control vs 34 (7.4%) treatment, p<0.001  
**Evidence:** Good Study, LOE1, Support (Criteria E1) |
| **Herlitz, J., 1988**  
**PRE-Thrombolytic Study**  
**Retrospective Study on the Goteborg Trial**  
1. Yes, the groups were clearly defined as per the Goteborg Trial  
2. There is no mention of blinding in the assessment of outcomes measures, but the outcomes measured were objective (namely, mortality).  
3. There is no mention of confounders  
4. Follow-up was at 2 and 5 years  
**Study Details:**  
- Design: Retrospective study on Goteborg metoprolol study (see below)  
- N = 1395 (697 to placebo and 698 to treatment arm)  
**Results:**  
- 2 year mortality: 17.2% in control arm vs. 13.2% in treatment arm, p = 0.04  
- Mortality over a 5 year period after initial randomization: 25.7% in control arm vs. 24.2% in treatment arm, p > 0.2  
**Subset of Patients Treated with <= 8 hours after onset of pain = median delay time in original study**  
- 2 year mortality: 17.3% in the control arm vs. 11.8 % in the treatment arm, p = 0.04  
- Mortality over a 5 year period after initial randomization: 25.3% in the control arm vs. 22.0% in the treatment arm, p > 0.2  
- Enzyme activities was lower in the treatment group than the control group, p = 0.03  
**Evidence:** Fair study, LOE3, Supportive (Criteria E2, E4) but subset analysis should be interpreted with caution. Also seems to show a trend that the earlier that patients are treated, the greater the benefit seen. |
| **Herlitz, J., F. Waagstein et al., 1997**  
**PRE-Thrombolytic Trial**  
1. Yes, comparison groups were clearly defined.  
2. Yes, outcomes were measured objectively in both groups.  
3. There is no mention of confounders.  
4. Patient follow-up was sufficiently long and complete for their goals.  
**Study Details:**  
- Design: post-hoc subgroup analysis of the Goteborg Trial (see elsewhere)  
- N = 262 (131 to placebo, 131 randomized to metoprolol)  
- Intervention: metoprolol 15 mg IV (ASAP after hospital arrival), then 50 mg, then 100 mg OD X 3 months, open label for the remainder of two years (within 48 hours of symptom onset)  
- Definition of mild-moderate CHF: SOBOE, diuretic use before randomization; ausculatory rales (no hypotension) |
### Results:
- No difference in clinical course during hospital stay
- 3 month mortality: 19% control vs 10% treatment arm, \( p = 0.036 \)
- 1 year mortality: 27% control vs 14% treatment, \( p = 0.0099 \)
- 3 month re-infarction rate: non-significant
- Symptoms of CHF/diuretic use at 3 mos: non-significant

### Evidence:
- Good study, LOE3, Supportive (Criteria E4)

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**Hjalmarson et al., 1983 (Goteborg Trial)**

**PRE-Thrombolytic Trial**


**The Goteborg Trial:**

1. Yes, assignment of patients was randomized
2. No randomization list was mentioned
3. All patients who were entered (including those who were subsequently withdrawn) were accounted for
4. Intention to treat is not explicitly described in the paper
5. The trial was double blinded (results at 3 months were done by physicians and statisticians not otherwise involved with the study)
6. Yes, the study gave guidance as to withdrawal criteria and treatment for varying complications.
7. Yes, the groups were similar at the start of the trial

**Study Details:**
- Design: double-blinded RCT
- \( N = 1395 \) (697 to placebo and 698 to treatment arm)
- Intervention: metoprolol 15 mg IV (*within 12 hrs*) followed by 200mg PO OD X 90 days (at which point all patients were allowed to receive open label metoprolol regardless of original treatment arm)
- Patients were given the treatment or control medication “as soon as possible” after having arrived at the hospital (but people were eligible if they came *within 48 hours* of supposed beginning of infarction)

**Results:**
- Primary endpoint was 3 month mortality: 62/697 (9%) deaths in control arm vs 40/698 (6%) deaths in treatment arm, \( p < 0.03 \) yielding a 36% reduction in mortality for treatment group i.e. 3 lives can be saved by treating 100 patients for 3 months on metoprolol; N.B. A Cox analysis was done to adjust for slight differences in baseline characteristics of the two groups yielding a \( p < 0.015 \)
  - Mortality difference maintained at 1 year (even though both groups openly received metoprolol at 3 months due to ethics of withholding treatment known to be beneficial post MI)
  - Values were similar across all age groups (values not published, but trend was stated to be similar to primary endpoint)
- Secondary endpoints: infarct size, arrhythmias, and tolerance
  - LDH values (suggestion of infarct size) were lower in treatment group (values not provided)
  - Ventricular fibrillation was seen in 17/697 control patients and 6/698 treatment patients (no \( p \) value provided)
  - Tolerance was judged to be good in both arms (19% were drawn from both groups)

N.B. Investigators noted that incidence of non-fatal and fatal infarct from days 4-90 were decreased by 35% in the treatment group (however, this was not pre-defined to be a primary or secondary endpoint)

**Evidence:** Good study, LOE1, Supportive for criteria E1 (but no \( p \)-value provided), E4, and E5 (but this finding is data derived and was not a pre-defined endpoint of the study)

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**International Collaborative Study Group, 1984**

**PRE-Thrombolytic Study**


1. Yes, patients were randomized to treatment groups within 4 hours of symptom onset and treated within 5 hours of symptom onset
2. There is no mention of how the randomization was done.
3. Yes, all patients were accounted for at the end of the study.
4. Yes, the investigators analyzed with the intention to treat.
5. The study was double blinded.
6. The authors make no mention of treatment differences other than placebo vs. timolol.
7. The patients were similar prior to the study

**Study Details:**
- Design: Double blinded RCT
- N = 144 (71 to placebo and 73 to treatment arm)
- Intervention: Within 4 hours of symptom onset, patients were randomized to either placebo or timolol (1 mg iv q10 min x 2 doses, followed by timolol iv infusion at 0.6 mg/hour x 24 hours, followed by timolol 10 mg po BID for the hospital stay

Results:
- Primary endpoint: infarct evolution and myocardial ischemia
  - Maximum cumulative CK release: decreased by 29.5% in the treatment group
  - QRS vector parameters: decreased 20-25% in the treatment group

Evidence: Good study, LOE1, Supportive (Criteria E2)

### PRE-Thrombolytic Trial


**ISIS-1**

1. Yes, the patients were randomized to treatment with atenolol vs. no treatment
2. Randomization was done by telephone but it is not clear whether the list was concealed. No placebo was used for the patients who were in the control group. The study designers argued that a) clinicians can easily guess that atenolol is the drug in question based on clinical effects on heart rate and blood pressure, and b) foregoing the placebo would make the study easier to adhere to, and c) the endpoint (vascular mortality) is a hard one and not likely to be swayed by clinicians knowing whether the patient was in the treatment or control arm
3. All patients were accounted for at the end of the trial
4. The investigators used intention to treat for all the groups
5. The RCT was unblinded (see reasons above), however the investigators in charge of following up on mortality rates were blinded to the treatment given
6. Aside from the atenolol treatment, the primary caregivers were instructed to treat their patients according to what they felt was appropriate (note: since the doctors of patients given atenolol knew that a beta blocker was already on board, the medications that used were likely affected by this knowledge; also, the patients who were given atenolol in the 7 day treatment period were more likely to be discharged on long term beta blockers vs. the control group)
7. Yes, the Table 1 shows similar group demographics

**Study Details:**
- Design: unblinded RCT
- N = 16027 (245 centres in 13 western European countries and Australia)
- Intervention: Atenolol 5-10 mg IV immediately, then 100 mg OD X 7 days within 12 hrs of the treating doctor diagnosing AMI (mean enrollment at 5 hrs)
- Control group did not receive the 7 days of atenolol in this manner (although the treating doctor could choose whatever medications he deemed appropriate for the patient)

**Results:**
- primary endpoint was death due to “vascular causes” (i.e. cardiac, cerebral, or any other vascular cause) as distinguished from “non-vascular” causes
  - Day 0-7 deaths = 365/7990 control vs 313/8037 treatment arm, p<0.04 (95% CI 1-27%) i.e. a 14% reduction in mortality at 7 days in the metoprolol group when compared to placebo; most improvement seen in days 0-1 (interestingly enough, the highest use of inotropes were also seen in days 0-1 in the treatment arm supposedly counteracting the resulting hypotension and shock post beta blockade)
  - Death at 1 year was 923/7990 control vs 825/8037 treatment arm, p<0.01
  - Non-fatal reinfarction was 161/7990 control vs 148/8037 treatment arm, non-significant differences
  - Non-fatal cardiac arrests was 198/7990 control vs. and 189/8037 treatment arm, non-significant difference
  - Rate of VF was not significant

N.B. Investigators combined the data with the MIAMI trial + 26 other smaller acute IV beta blocker studies described by Yusuf (see below)
- Day 0-7 mortality 586/13721 control v. 513/13815 2p<0.02
- Day 0-7 death, re-infarction, VF 1312/13721 control vs 1127/13815

**Evidence:** Good study, LOE 1, supportive (criteria E4, mortality at 7 days and 1 year with ISIS-1 study alone but not at the end of the study on January 1, 1985); when combined with MIAMI and smaller beta blocker trials there is some support for mortality benefit, re-infarction reduction, and reduced incidence of VF)
**PRE-Thrombolytic Trial**

**ISIS-1 Retrospective Analysis (based on 1986 original study)**

1. Yes, the two groups that were compared were the patients who received atenolol vs. the ones who were not administered atenolol in the first seven days post MI (note: these two comparison groups were all patients who had died during day 0-1)
2. The cardiologist reviewing the clinical reasons for death during days 0-1 was blinded to whether the patient was in the treatment or control arm
3. There is no mention of confounders.
4. The retrospective study was done years after ISIS-1 was published. And the follow-up was sufficiently long since all the patients being studied died on days 0-1.

**Study Details:**

- Retrospective chart review of patients enrolled in ISIS-1 who died on days 0-1 (specifically, from Great Britain, Ireland, Denmark, Norway, Sweden, and Finland only—these countries supposedly had the most accessible and complete records out of the original 14 participating countries)
- N=193 (out of a possible 217 eligible patients, 193 records were accessible; out of the 193 records, 79 had been allocated to atenolol while 114 had been in the control group; there is no comment as to why the other records were not accessible)
- see ISIS-1 analysis above for details of the study

**Results:**

- Total deaths (in the above countries only): 126/6101 control vs. 91/6121 treatment arm; 2p<0.01
- Cardiac rupture (on necropsy): 17/114 control vs. 5/91 treatment arm, 2p<0.01
- Cardiac rupture (on necropsy) + incidence of electromechanical dissociation (presumed to be b/c of cardiac rupture): 54/114 control vs. 20/91 treatment arm, 2p<0.02
- VF with death: 13/114 control vs. 5/91 treatment arm, not significant
- Bradycardia with death: 3/114 control vs. 10/91 treatment arm, not significant
- Left ventricular failure: 13/114 control vs. 6/91 treatment arm, not significant
- Shock with death: 24/114 control vs. 34/91 treatment arm, not significant

**Evidence:** Fair study, LOE 3, Supportive (Criteria E4 but only for the first day as noted in ISIS-1, E7)

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**Jurgensen, HJ., MP Andersen et al., 1984**

**PRE-Thrombolytic Study**

1. Yes, patients were randomly assigned to treatment groups.
2. It is unclear how randomization was achieved.
3. No patients were lost to followup
4. The authors used intention to treat to analyze their data
5. Yes, this is a double blinded trial.
6. Other than the experimental treatment, patients were treated according to routine practice of the admitting department (ie. the same in each group).
7. The patients were different at the start of the trial (LV failure and cardiac arrest resuscitation was more prominent in the control group and in the <65 age group more patients in the alprenolol group experienced a true MI)

**Study Details:**

- Design: Double blind stratified RCT
- N = 480 (242 placebo vs. 238 treatment group)
- Intervention: alprenolol 5 mg iv over 5 min x 2, then 3 hours later alprenolol 200 mg po BID (immediately after arrival to CCU)

**Results:**

- Primary endpoints:
  - Total mortality at 28 days: Not discussed
  - Totally mortality at 12 months: Not discussed
- Secondary endpoints:
  - Enzymatic myocardial infarct size (used CK): 51% reduction in median peak CK in MI patients < 65 years when treated within 12 hours (no benefit seen if > 65)
  - Arrhythmias: significant decrease in VF and VT in patients < 65 years with first MI (14.7% control vs. 3.3% treatment arm) and patients > 65 with reinfarction (33.3% in control arm vs. 3.7% in treatment arm)

**Evidence:** Good study, LOE 1, Primary endpoints not discussed, Support for secondary endpoints (Criteria E1, E2)
Malmberg, K., J. Herlitz, A. Hjalmarson et al., 1989
(Retrospective study on Goteborg and MIAMI trials)

**PRE-Thrombolytic Trial**


**Retrospective Study of Goteborg and MIAMI**

1. Yes, comparison groups had previously been defined in the original Goteborg and MIAMI metoprolol studies (both double blinded RCTs well known in the literature). Within these studies, the author of this retrospective study was trying to see what the effect was on the subgroup of patients with diabetes in the above studies.
2. In the original Goteborg and MIAMI studies, the outcomes were measured in a blinded fashion.
3. The authors of this paper do not mention any confounders for patients with diabetes.
4. Patients were followed in a sufficiently long and complete manner in the original studies.

**Study Details:**
- Retrospective subgroup analysis of patients with diabetes enrolled in the Goteborg and MIAMI trials
- N = 120/139 patients in the Goteborg Trial and 413/5778 patients in the MIAMI trial had diabetes

**Results:**

**Goteborg**
- Mortality at 3 months: 7.5% in control arm and 17.9% in treatment arm
- Late infarction: 16.4% in control arm and 3.8% in treatment arm

**MIAMI**
- Mortality at day 15: 5.7% in control arm and 11.3% in treatment arm
- Late infarction by day 15: 4.5% in control arm vs. 3.1% in treatment arm

**Evidence:** Good study, LOE3, Supportive of E4 in diabetic patient subgroups

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*Miami, 1985*

**PRE-Thrombolytic Trial**


**MIAMI**

1. Yes, patients were randomized to control or treatment within 24 hrs of symptoms suggestive of ACS as soon as possible after being admitted to the CCU
2. Yes, the randomization list was concealed. Patients were assigned a consecutive randomization code that was stratified at the trial centre by a microcomputer manned by one independent committee member not otherwise involved with the study. Four sets of the randomization list were made.
3. There is no mention of patients being lost at the end of the treatment period of 15 days
4. Once the treatment medication ampoule was broken, patients were considered randomized regardless of whether they received full, partial, or no medication/placebo. 24 control and 15 treatment patients did not receive any medication after being randomized. The implication is that the investigators used intention to treat in the analysis, but this is not stated explicitly.
5. Yes, MIAMI is touted as a double blinded study (although the extent to which treating doctors could determine from the patient’s vital signs that they were indeed treating with a beta blocker is presumably high).
6. The groups were not treated equally. Each participating hospital had clear guidelines when to give reduced quantities of medication or when to withdraw patients completely. And each hospital was instructed to give otherwise “standard” medical care to their patients. However, patients in the treatment arm were generally instructed to not receive exogenous beta blockers, verapamil, and diltiazem.
7. The two groups were similar at the start of the trial. However, the randomized group was quite different (younger and including more males) than the eligible group of patients who did not meet the 14 exclusion criteria (50% because already on beta blocker/calcium channel blockers).

**Study Details:**
- Design: double blinded RCT
- N = 5778 (chosen from an eligible group of 26439 patients from 17 countries and 104 centres)
- Intervention = metoprolol 5 mg IV q2 min x 3 within 24 hrs symptom onset (in the CCU), then 50 mg po q6hrs x days 0-2, then 100 mg PO q12 hrs for days 3-15 (then all patients received open label metoprolol after the treatment period of 15 days)
- 25% of patients were recruited within 4 hours and the remaining 75% were recruited within 12 hours of symptom onset (although patients were eligible up to 24 hours from symptom onset)

**Results:**
- Primary endpoint: death 142/2901 control group vs 123/2877 treatment arm at day 15; p = 0.29
- Retrospective studies:
**Worksheet No. ACS-023A.doc**

<table>
<thead>
<tr>
<th>Study Details</th>
<th>Study Results</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Murray, DP., RG. Murray et al., 1988</strong></td>
<td>&quot;high risk group&quot; 87/1027 deaths in control arm vs 61/1011 treatment arm at day 15; p = 0.033 (high risk patients pre-defined as having &gt;/ 3 of: age &gt; 60 years, ECG signs of MI, hx MI, HTN, angina pectoris, CHF, DM, acute or chronic Rx with diuretics or cardiac glycosides); p value must be interpreted with caution -no difference in mortality when analyzed within “low risk group” (&lt; 2 pre-defined risk factors) -Subgroups: no subgroups were found to be inherently affected (either positively or negatively) by treatment with metoprolol -Re-infarction differences difficult to determine based on lack of gold standard of when treatment given (pre-randomization the two arms seemed equally distributed as to “probable” and “suspected” MI while after randomization 70.5% of treatment arm vs. 72.4% of control arm were eventually classified as “definite MI”); overall there seemed to be a trend that the earlier metoprolol was given (i.e. before a definite MI has been established), the greater the effect of the drug with almost no effect being seen if given after 8 hours -Enzymatic estimation of infarct size: 4.9 arbitrary units for control arm vs. 4.6 arbitrary units for treatment arm, p = 0.072 -No difference in ventricular dysrhythmia: -VF occurred in 52 patients in control arm vs 48 in treatment arm (for a total of 96 and 67 VF overall episodes respectively), non-significant -VT 40 in control arm vs 37 treatment arm, non-significant -Differences in SVT -Atrial fibrillation/Atrial flutter seen in 298 control arm vs 238 treatment arm, p&lt;0.01 -other SVT 265 control arm vs 125 treatment arm, p &lt;0.001</td>
<td>Good study, LOE1, Neutral (Criteria E1, E2, E4—but mortality measured at 15 days at the end of the treatment period)</td>
</tr>
<tr>
<td><strong>Owensby, DA, 1985</strong></td>
<td>Murray, DP., RG Murray et al (1988). “Does acute-phase beta-blockade reduce mortality in acute myocardial infarction by limiting infarct size?” International Journal of Cardiology 20:327-339.</td>
<td>Note: This study was a subset of patients enrolled in the MIAMI trial (Birmingham centre). The only difference was added measurements concerning ECG QRS scoring systems, peak enzyme release, and myocardial perfusion defect size. Otherwise, it held to the standards set for the study design of MIAMI. Study Details: -subset of MIAMI study -N = 129 (64 to control arm, 54 to treatment arm) -Intervention: as with MIAMI Results: Primary endpoints: -close correlation between the three methods to estimate infarct size (although limitations of enzyme peak were acknowledged) -peak enzyme release (AAT and LD): decreased in the treatment group by 11% and 7% respectively -ECG QRS scoring systems: non-significant -Thallium 201 perfusion defect (done on 49 of the patients distributed as 24 in control arm and 25 in treatment arm): non-significant</td>
</tr>
<tr>
<td><strong>PRE-Thrombolytic Trial</strong></td>
<td>Owensby, DA. (1985). “Failure of intravenous pindolol to reduce the hemodynamic determinants of myocardial oxygen demand or enzymatically determined infarct size in acute myocardial infarction.” Aust NZ J Med 15:704-711.</td>
<td>1. Yes, patients were randomized to treatment. 2. Yes, the randomization list was concealed by a sealed envelope method. 3. There is no mention of patients being lost to the study 4. There is no specific mention of not using intention to treat. 5. Yes, this is a blinded study. 6. Yes, patients were treated “as necessary”, no treatments were specifically withheld. 7. Yes, the groups were similar at the start of the trial.</td>
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<tr>
<td>Primary endpoint:</td>
<td>1. Yes, comparison groups were clearly defined.</td>
<td></td>
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<tr>
<td>Enzyme derived infarct size:</td>
<td>2. There is no mention whether the outcomes were measured in a blinded fashion but they were measured the same in both groups.</td>
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<tr>
<td>non-significant</td>
<td>3. There is no mention of confounders.</td>
<td></td>
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<tr>
<td>Evidence: Fair study, LOE1, Neutral (Criteria E2)</td>
<td>4. Yes, follow-up was sufficient.</td>
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</table>

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Design: Retrospective analysis of a subgroup of patients in the VALIANT registry</td>
<td>Study Details:</td>
</tr>
<tr>
<td>N = 5391 (in VALIANT registry) of which N = 306 experienced sustained VT/VF</td>
<td>-Design: prospectively planned post-hoc observational analysis, RCT</td>
</tr>
<tr>
<td>Intervention: acute beta blockade either iv or po within 24 hours of symptom onset</td>
<td>-N = 41 021</td>
</tr>
<tr>
<td>Results:</td>
<td>-Intervention: atenolol 10mg iv “as soon as possible” after enrollment, then 100mg po od N.B. This is an observational study, thus timing of atenolol dosing quite varied</td>
</tr>
<tr>
<td>authors made adjustments for baseline characteristics, propensity for beta blocker use, and interaction between Killip classification and use of beta blockers</td>
<td>-Patients were enrolled in one of four lytic strategies:</td>
</tr>
<tr>
<td>in house mortality was decreased in subset of patients having sustained VT/VF if they had been treated with beta blockers within 24 hours, RR 0.28 95% CI 0.1-0.75, p = 0.013 without evidence of further CHF)</td>
<td>-SK + SQ UFH</td>
</tr>
<tr>
<td>Evidence: Fair study, LOE3, Supportive (E4)</td>
<td>-SK + IV UFH</td>
</tr>
<tr>
<td>Pfisterer, M., JL Cox et al., 1998 POST-Thrombolytic Trial</td>
<td>-tPA + IV UFH</td>
</tr>
<tr>
<td>Evidence: Fair study, LOE3, Supportive (Criteria E4 with po fewer deaths than iv/iv and po, E6)</td>
<td>-SK + tPA + IV UFH</td>
</tr>
<tr>
<td>Results:</td>
<td>Results:</td>
</tr>
<tr>
<td>30 day mortality</td>
<td>-No atenolol vs any atenolol OR 0.20 (95% CI 0.19-0.22); adjusted OR 0.29 (95% CI 0.26-0.32)</td>
</tr>
<tr>
<td>-iv + po vs only po OR 1.2 (95% CI 1.0-1.3); adjusted OR 1.2 (95% CI 1.1 -1.5)</td>
<td>**No mortality difference between iv and po vs only po given on D1/2 if adjusted for baseline differences</td>
</tr>
<tr>
<td>**No mortality difference between iv and po vs only po given on D1/2 if adjusted for baseline differences</td>
<td>-No difference in re-infarction</td>
</tr>
<tr>
<td>-no iv (4.1%) vs iv (3.9%), p = 0.61</td>
<td>-no iv (4.1%) vs iv (3.9%), p = 0.61</td>
</tr>
<tr>
<td>-iv + po (3.8%) vs. po (4.2%), p = 0.07</td>
<td>-iv + po vs only po OR 1.2 (95% CI 1.0-1.3); adjusted OR 1.2 (95% CI 1.1 -1.5)</td>
</tr>
<tr>
<td>-any atenolol vs. no early atenolol OR 1.02 (95% CI 0.90 to 1.15)</td>
<td>**No mortality difference between iv and po vs only po given on D1/2 if adjusted for baseline differences</td>
</tr>
<tr>
<td>Cardiac Tamponade:</td>
<td>-Cardiac Tamponade:</td>
</tr>
<tr>
<td>-No IV (0.9%) vs. IV (0.6%), p &lt; 0.0001 (but 0.5% incidence in patients receiving only PO)</td>
<td>-No IV (0.9%) vs. IV (0.6%), p &lt; 0.0001</td>
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<tr>
<td>-CHF:</td>
<td>-CHF:</td>
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<tr>
<td>-iv (14.3%) vs po (within 24 hrs) (10.7%), p &lt; 0.01</td>
<td>-iv (14.3%) vs po (within 24 hrs) (10.7%), p &lt; 0.01</td>
</tr>
<tr>
<td>-Cardiogenic shock:</td>
<td>-Cardiogenic shock:</td>
</tr>
<tr>
<td>-iv (3.3%) vs po (within 24 hrs) (2.2%), p &lt; 0.01</td>
<td>-iv (3.3%) vs po (within 24 hrs) (2.2%), p &lt; 0.01</td>
</tr>
<tr>
<td>Evidence: Fair study, LOE3, Supportive (Criteria E4 with po fewer deaths than iv/iv and po, E6)</td>
<td>Evidence: Fair study, LOE3, Supportive (Criteria E4 with po fewer deaths than iv/iv and po, E6)</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
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<tr>
<td>Rehnqvist, Olsson et al., 1987 (PRE-Thrombolytic Trial) Subset of MIAMI</td>
<td>Retrospective subgroup analysis of an original double blinded RCT (MIAMI)</td>
</tr>
<tr>
<td>Risenfors, M., J. Herlitz et al, 1991 (POST-Thrombolytic Study Including Pre-Hospital Component)</td>
<td>Blinded RCT, 2x2 factorial set up (first patients randomized to thrombolysis and then further randomized to iv metoprolol)</td>
</tr>
<tr>
<td>Roberts, Rogers et al. 1991 (Post-Thrombolytic Trial)</td>
<td>An RCT designed to test whether patients did better if randomized to an invasive strategy (routine angiography and PTCA as indicated at 18-48 hours) vs. conservative strategy (angiography for possible angioplasty if certain pressing clinical conditions were met) after having received rt-PA/heparin/ASA (ie. All TIMI II patients had been thrombolysed upon suspicion/confirmation of MI based on &gt;30 minutes of chest pain and supportive ECG findings). TIMI-IIb was a subset study of the TIMI II trial to determine whether early IV use of metoprolol had a benefit vs. delayed metoprolol administration.</td>
</tr>
</tbody>
</table>
blocker study. These patients were randomized to early or delayed IV metoprolol treatment.

2. It is not clear if the randomization list was concealed or how the randomization was done. The article just says “randomized”.
3. All patients were accounted for at the conclusion of the study
4. The study data was analyzed using intention to treat.
5. Patients who were treated immediately with metoprolol were obvious to the clinician. There was no attempt to give patients randomized to the delayed treatment arm a placebo to blind the treating physician. However, the endpoints were analyzed by physicians blinded to the treatment arm.
6. Non study beta blocker was discouraged unless thought to be absolutely indicated by the treating physician. Therefore, the delayed treatment arm received overall slightly more non-study beta blocker than the immediate treatment arm. Otherwise, the two groups were treated equally.
7. The two groups had similar baseline characteristics as demonstrated by Table 1.

**Study Details:**
-N=1434
-Design: Unblinded RCT substudy within another RCT (TIMI II) i.e. a 2x2 factorial study design

<table>
<thead>
<tr>
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<th>Invasive Strategy Post rt-TPA</th>
<th>Conservative Strategy Post rt-TPA</th>
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</thead>
<tbody>
<tr>
<td>Immediate Beta Blocker</td>
<td>366</td>
<td>354</td>
</tr>
<tr>
<td>Delayed Beta Blocker</td>
<td>365</td>
<td>349</td>
</tr>
<tr>
<td></td>
<td>731</td>
<td>703</td>
</tr>
<tr>
<td></td>
<td>1434</td>
<td>1434</td>
</tr>
</tbody>
</table>

-immediate intervention: metoprolol 5 mg IV q2min x 3 within 4 hrs post rtPA, then 15 minutes after the last IV dose patients were given 50 mg PO q12hrs x 24 hrs, then 100 mg PO q12 hrs from then on (note: page 424 describes how the patients' vital signs were monitored and how the metoprolol dose was adjusted or withheld according to patients' reactions to the medications)

-not specifically stated within which time the metoprolol was started (just done as soon after initial randomization to invasive and conservative strategies was made)

-delayed intervention: 50 mg PO BID on day 6 (at least 48-72 hours before the radionuclide ventriculogram), then 100 mg PO BID for the rest of the study involvement as tolerated

**Results:**
-Primary endpoint: no differences in LVEF at d/c and at 6 week follow-up between the two groups
-Pre-defined secondary endpoints (see Table 6 on page 430 and Table 8 on page 431):
  -No difference in death at 6 days, 6 wks, and 1 yr
  -Total mortality at 6 weeks was 3.5% in control vs. 3.6% in treatment group; at 1 year the values were 5% and 4.8% respectively (N.B. in the subset pre-defined as “low risk” there was a reduced total mortality to those randomized to immediate treatment-see page 432)
  -Non-fatal re-infarction at 6 days 33/714 control vs 17/720 treatment group, (p=0.02)
  -Non-fatal re-infarction at 6 wks 46/714 control vs 28/720 treatment arm, (p=0.03)
  -Recurrent chest pain at 6 days 170/714 control vs 134/720 treatment arm, (p=0.02)
  -No statistical difference in incidence of ICH but trend towards benefit in group receiving immediate β-blocker

N.B. Although secondary endpoints were pre-defined, the investigators deemed that a p=0.01 would support true significance vs. chance results in such small subgroups).

Bottom Line: The study does not support any definite benefit of administering beta blockers earlier than later. However, in appropriate post-infarction patients, beta-blockers are safe when given early after thrombolytic therapy and may be associated with slight incidences of decreased myocardial ischemia, chest pain, and re-infarction in the early post-recovery period. However, there is no benefit of early vs. late administration in improving ventricular function or reducing overall mortality.

**Evidence:** Good study, LOE 1, neutral support to study question, Criteria C, E5, E9 (lower trend of ICH in immediate metoprolol group, but non-significant)

1. Yes, the patients were randomized to either the treatment arm (metoprolol) or placebo.
2. The study does not specify how the randomization list was produced nor whether it was concealed to the treating doctor.
3. Some of the patients included in the study were not accounted for at the end. Of 800 patients who were accepted, 416 were assigned to the treatment arm while 348 were assigned to the placebo arm yielding a total of 764 patients eventually treated. 2 patients who were initially enrolled declined further treatment. However, it is not known what happened to the remaining 34 patients. Of the 746 patients included in the study, 2 of the treatment group patients were lost to follow-up vs. 1 patient in the placebo arm.
4. The investigators analyzed the data using intention to treat.
5. It is unclear whether the doctor who gave the initial intervention was blinded. There is no specific mention about whether the investigators analyzing the data were blinded.
6. The enrolled patients were admitted to the CCU and treated with a “routine ward protocol” during the length of stay in hospital. However, any other beta blocking agents as well as verapamil were avoided in patients continuing on the treatment drug.
7. Yes, the groups were similar at the start of the trial (see Table 1).

**Study Details:**
- Design: Unblinded RCT
- N = 764 (416 to treatment arm, 348 to placebo arm); this N was chosen by the investigators as the number needed to show with 50% confidence that a true reduction in mortality of 30% at one year existed at a significance level of 5%)
- Intervention: Patients suspected of having an MI were either given the treatment intervention (metoprolol 15 mg IV over 5 minutes followed by metoprolol 50 mg po q6hrs x 48 hours then 100 mg PO q12 hrs x 1 year) or similar looking placebo tablets
- Patients received treatment “after initial assessment” (either at home, when seen by the Mobile Coronary Care Team, or in hospital)

**Results:**
- Primary endpoints were total mortality/cardiac mortality/sudden death in 3 situations (in hospital, at 3 months, and at 12 months)
  - Total mortality at discharge was 5.2% for control vs. 6% in treatment arm, non-significant
  - Total mortality at 3 months was 9.1% for control vs. 8.7% in treatment arm, non-significant
  - Total mortality at 12 months was 13.6% for control vs. 11.9% for treatment arm, non-significant
  - Cardiac causes of death was not significantly different for both groups (no statistics given for these findings)
  - Incidence of sudden death at 1 year was 4.7% for control vs. 1.9% in the treatment arm (p < 0.05); these were patients who continued on metoprolol for the year and could reflect the known benefit of long-term remodeling of beta blockers rather than the effect of early treatment with beta blockers
  - Pre-defined subgroup analyses (anterior MI, inferior MI, age > or < 65, timing of when patient seen vs. when treated) did not yield any significant findings

**Evidence:** Fair study, LOE1, Neutral (Criteria E4 was shown to be supportive but this effect cannot necessarily be attributed to early beta blocker treatment vs. long term beta blocker treatment post MI)

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**Yusuf, Peto et al. 1985**

**PRE-Thrombolytic Review Paper**


**Meta-analysis**
1. Yes, this review was aimed at consolidating all of the smaller beta blocker trials before 1985 (oral and IV, short and long term use) used for treating MI to see if there were any consistent results regarding mortality and morbidity in humans.
2. No, the study design was not defined.
3. The authors did not state their inclusion and exclusion criteria but were very comprehensive in their review.
4. Yes, inclusive searches were used (formal searching, hand searching, personal knowledge of peers on trials that had been done but not published etc. were included)
5. Characteristics of each study (e.g. exclusion criteria, timing of treatment, duration of treatment, endpoints etc.) were indicated. But there is no mention of methodological quality of each trial.
6. They do not state that any studies were excluded (there are 143 references included)

**Study Details:**
- Design: Review paper
- 143 papers reviewed for the effects of morbidity and mortality in human trials testing the effect of short and long term beta blockers in the acute and long term setting post-MI
Results:
- Short term po beta blockade (administration <4 hrs since chest pain to <72 h since chest pain; duration 3 min to 28 d): total mortality 165/1900 beta-blocker vs 165/1711 control; non-significant
- Short term iv beta blockade (administration <6hrs to <24 hrs; duration 72 hrs to 16 days): 1 week mortality 194/5676 beta blocker vs 205/5633 control; non-significant
- SFx:
  - Early entry PO: incidence of CHF 943/5395 beta blocker vs 904/5380 control; non-significant
  - Early entry IV: incidence of CHF 157/1513 beta blocker vs 145/1330; non-significant
  - Hypotension (pooled early PO + IV): 148/4681 beta blocker vs 144/4697 control; non-significant
  - Heart block (pooled early PO + IV): 266/6235 beta blocker vs 256/6089; non-significant

Evidence: Good paper, LOE1, Neutral (Criteria E4, E9)