# Are lipophilic beta-blockers preferable for peri-operative cardioprotection?

## *Implications from a limited systematic review of the efficacy of atenolol and metoprolol in preventing in-hospital ventricular fibrillation following acute myocardial infarction.*

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**Abstract**

Atenolol has been proposed as a peri-operative cardioprotective agent in patients with coronary disease. However, recent reports have cast doubt over the cardioprotective efficacy of atenolol in patients with hypertension and coronary artery disease. There is therefore doubt whether atenolol is the correct cardioprotective drug in the surgical setting. It is possible that some of the physiochemical properties of atenolol (hydrophilic and cardioselective) may decrease it's efficacy in comparison to its more lipophilic congeners (such as propranolol, metoprolol, bisoprolol and carvedilol). The issue of prevention of perioperative cardiac events is complicated by many confounders. As a result, the role of the physicochemical properties of beta-blockers can only be determined in the simpler setting of myocardial infarction. Therefore, we conducted a restricted systematic review to evaluate the effect of initiating atenolol and metoprolol on the prevention of ventricular fibrillation following acute myocardial infarction. Neither atenolol nor metoprolol significantly decreased the incidence of in-hospital ventricular fibrillation following acute myocardial infarction. The number-needed-to-treat to prevent in-hospital ventricular fibrillation equals or exceeds 200 with metoprolol and atenolol respectively. Based on the findings of this systematic review and the recently published Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT), it can be concluded that the prevention of peri-operative myocardial ischaemia with a beta-blocker is clinically more important to peri-operative cardioprotection than whether the beta-blocker is lipo- or hydrophilic.

**Keywords:** Atenolol, metoprolol, myocardial infarction, ventricular fibrillation.

### Introduction

There has been considerable enthusiasm for the use of atenolol as a cardioprotective agent in both acute medical patients,[1] and in the peri-operative period in patients with high cardiac risk factor scores.[2] Indeed, in 1997 atenolol was specifically proposed for protection against peri-operative cardiac complications in patients with coronary disease by the American College of Medicine.[3]

However, atenolol is now under increasing scrutiny as it has been shown to be ineffective in the long-term management of hypertension and post myocardial infarction.[4-6]

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These reports suggest that the cardioprotective efficacy of atenolol, a hydrophilic, cardioselective beta-blocker[4-6] may be less than that of lipophilic congeners (such as propranolol, metoprolol, bisoprolol and carvedilol). A meta-analysis of studies in hypertensive medical patients showed no difference in cardiovascular outcome when atenolol was compared with placebo, but a higher mortality when compared with other antihypertensives.[4] Similarly, the ASCOT trial in hypertensive patients has been discontinued because the amlodopine and perindopril arm had a better cardiovascular outcome than the atenolol and bendroflumethiazide arm.[7] In meta-analyses of beta-blocker studies following myocardial infarction (MI), atenolol was also shown to be less efficacious than other beta-blockers. Soriano et al showed that survival was associated with beta-1 selectivity, lipophilicity, and the absence of intrinsic sympathomimetic activity (ISA).[5] Metoprolol, with many of these desirable properties, had the greatest benefit (RR 0.83 (95% CI 0.72-0.96)) in comparison to atenolol (RR

0.95 (95% CI 0.88-1.02)) and propranolol (RR 0.85 (95% CI 0.74-0.98)).[5] In a subsequent meta-analysis, the only beta-blockers shown to decrease mortality post MI were all lipophilic (propranolol, timolol, metoprolol, acetabutolol). Again, the effect of atenolol on mortality did not reach statistical significance.[6] It is therefore debatable whether atenolol is cardioprotective following MI in medical patients.[6] A large retrospective chart review of patients surviving acute MI however showed similar two year survival rates between nearly 18 000 atenolol and 45 000 metoprolol treated patients.[8] There are no other studies which directly compare common outcomes in lipophilic and hydrophilic beta-adrenergic antagonists following MI.

Carvedilol (another lipophilic agent) also shows survival benefit in patients with congestive heart failure (CHF) and associated coronary artery disease (RR 0.65 (95% CI 0.56-0.75)).[9-14]

It is possible that the physiochemical properties of specific beta-blockers are important in ensuring cardioprotection (Table 1).

**Table 1. Ancillary properties of selected beta-blockers in current use[9]**

| Beta-blocker | β-1 selectivity | α-blockade | Lipophilicity | ISA |
|---|---|---|---|---|
| Propranolol | No | No | Yes | No |
| Esmolol | Yes | No | No | No |
| Bisoprolol | Yes | No | Yes | No |
| Carvedilol | No | Yes | Yes | No |
| **Atenolol** | **Yes** | **No** | **No** | **No** |
| **Metoprolol** | **Yes** | **No** | **Yes** | **No** |

ISA: intrinsic sympathomimetic activity

The cardioprotective efficacy of atenolol,5, 6,15 metoprolol[5, 6 ,16] and bisoprolol[5, 6, 17] in medical patients is shown in Table 2. While atenolol,[18,19] metoprolol[20-22] and bisoprolol[23] are commonly used for peri-operative cardioprotection, only metoprolol has proven efficacy in patients with a history of MI or CHF (Table 2). There may be some doubt therefore about the appropriateness of atenolol as a cardioprotective agent in the peri-operative period. Importantly, one may also question the cardioprotective efficacy of esmolol, the other beta-blocker which is used for peri-operative cardioprotection[24, 25] as it has similar physiochemical properties to atenolol (Table 1).

**Table 2. The effect of various beta-blockers on survival post myocardial infarction and in congestive heart failure in medical patients.**

| | Post myocardial infarction | Congestive heart failure |
|---|---|---|
| Atenolol | No efficacy in meta-analyses[5 6] | Efficacy proven in small studies[15] |
| Metoprolol | Efficacy in meta-analyses[5 6] | Efficacy in single large RCT[16] |
| Bisoprolol | No data available[5 6] | Efficacy in meta-analysis[17] |

The peri-operative evidence of the efficacy of beta-blockers is inconclusive (Table 3). In the largest systematic review and meta-analysis of the randomised, placebo-controlled trials of acute peri-operative beta-blockers in non cardiac surgery, it has been shown that the sample size is too small to draw a conclusion.[2] It is calculated that 6124 patients are needed to detect a 25% reduction in adverse cardiac events (where the control group has an adverse event rate of 10%). At present only 1152 patients have been identified from placebo-controlled randomised trials.[2] A recent analysis of prospective observational and case control studies suggests that chronic beta-blockade affords little or no cardiovascular protection in the peri-operative period.[2,6] If atenolol does not offer similar cardioprotection (in comparison to other beta-blockers) in medical patients, then this may be a confounder in the outcomes of the various peri-operative studies. If this were true for the peri-operative period, then the anaesthetist may need to rethink his present strategy with regard to beta-blocking agents.

**Table 3. The relative risk ratios and 95% confidence interval for the efficacy of acute and chronic beta-blocker administration on peri-operative outcome.**

| Peri-operative beta-blockers | Peri-operative cardiac mortality | Peri-operative non-fatal myocardial infarction | Myocardial ischaemia |
|---|---|---|---|
| Acute administration | 0.40 (0.14-1.15)[2] | 0.38 (0.11-1.29)[2] | 0.40 (0.26-0.61)*[50] |
| Chronic administration[26] | 0.80 (0.56-1.15) | 2.14 (1.29-3.56) | 1.10 (0.76-1.57) |

*Both intra- and postoperative ischaemia

Although the efficacy of atenolol is controversial in the long-term management of hypertension,[4] as anaesthetists it is necessary that we ascertain the cardioprotective efficacy of atenolol during acute coronary events characteristic of peri-operative cardiac complications. It has been suggested that beta-blockers that are lipophilic are more efficacious in the prevention of life-threatening arrhythmias,[9] and this may partly explain why atenolol has no proven survival benefit following MI.[5, 6] Prevention of ventricular fibrillation may therefore be considered a simple clinical model of the cardioprotective efficacy of a beta-blocker following an acute MI. In an attempt to address the importance of these physiochemical properties, we have conducted a restricted systematic review to answer the following question; 'Is there a difference in the efficacy in preventing in-hospital ventricular fibrillation following admission for acute myocardial infarction between atenolol (a hydrophilic beta-blocker with no proven survival benefit following MI) and metoprolol (a lipophilic beta-blocker with proven survival benefit following MI)?'

We have not included data from the peri-operative literature; as Devereaux et al[2] have recently indicated that the total sample size of all randomised controlled trials in this population is too small to make a conclusive outcome decision on all adverse cardiac events, and hence it is also impossible to analyse data for a single cardiac outcome (ventricular fibrillation) from the current peri-operative literature.

If the medical (non-peri-operative) literature shows that atenolol is less cardioprotective than metoprolol in this systematic review, then we would suggest that the use of peri-operative atenolol is reconsidered.

## Methods

In order to evaluate the effect of initiating metoprolol and atenolol treatment on the prevention of ventricular fibrillation following myocardial infarction, a Medline search restricted to 1980 to 1986 was conducted. The reason for the limited search was the following; firstly and most importantly to exclude a number of complex and confounding effects of other medical therapies commonly used for management of acute MI today, which would make interpretation of the cardioprotective efficacy of the beta-blocker studied (atenolol or metoprolol) difficult; secondly, during this time period beta-blockers were being investigated as the major agents for the management of acute MI; thirdly, the two large multicentre trials of atenolol and metoprolol following myocardial infarction were published at this time;[1, 27] fourthly we chose to identify studies where the controls did not have beta-blockers administered (this would be unlikely in current medical practice, yet possible in surgical patients where acute beta-blockade has been initiated for peri-operative cardioprotection); and finally by limiting the years of the search, the medical therapy received by the patients in the studies identified could be considered comparable.

We searched for randomised controlled trials which reported the effects of beta-blockers on short-term in-hospital cardiac outcomes in medical patients following myocardial infarction. Only data for the beta-blockers atenolol and metoprolol were analysed.

The reference lists of eligible trials (and systematic reviews) were also examined for further relevant trials. The terms used in the search strategy were: beta-adrenergic antagonists; cardiovascular system, effects; complications, arrhythmias; myocardial infarction. We excluded trials where there were no outcome events (ventricular fibrillation) in the either the control or treatment groups. Where data publication was replicated, we used the publication which contained the largest number of subjects. We did not exclude trials in which no placebo was given to the control group, as during this time period, a placebo was not considered necessary in studies examining mortality.[1]

Only data from human studies, published in the English language, are included in this review. The data abstracted from the trials included the numbers of patients randomised to beta-blocker or placebo/control group (on an intention to treat basis), the number of patients with reported in-hospital ventricular fibrillation, and the markers of validity of all trials included.

Statistical methods. Data from the different studies were collated in binary form with reference to drug therapy and outcome. The results were analysed to calculate relative risk ratios and their 95% and 99% confidence intervals (and two-tailed p-values) using STAT-SAK v2.50 (GE Dallal, 1985-1991; Malden MA 02148). To correct for differences in sample size of the various studies, the weighted risk reduction was calculated with a weighting proportional to the total size of the study. Heterogeneity within the different studies of each beta-blocker was assessed using a 4 x n contingency method, where n=number of studies in the individual meta-analysis tables. Results were calculated as a Chi-squared statistic, and significance determined for 3 x (n-1) degrees of freedom; again using STAT-SAK v2.50. To determine the sample sizes of studies to achieve significant results at the 5% level with >80% power, the summated outcomes for the individual drug therapies were analysed using PC-Size in CONSULTANT v1.0 (GE Dallal, 1990; Malden MA 02148).

## Results

Literature searching revealed 345 publications. Three-hundred and five publications were excluded for the following reasons; 182 trials included beta-blockers other than atenolol or metoprolol and/or other concomitant medical therapy, 45 studies did not record ventricular fibrillation as an outcome, 14 studies included other interventions in addition to beta-blockade, 21 studies had indications other than acute MI for administration of beta-blockers and 43 papers were reviews or retrospective publications. Of the remaining publications, eight eligible randomised studies were identified[1, 27-33] and 32 duplicate publications. The quality measures[2] of these trials [27-33] are shown in Table 4.

**Table 4. Quality measures of the randomised controlled trials**

| Trials | Concealment of randomisation | Trial stopped early | Patients blinded | Healthcare providers blinded | Data collectors blinded | Outcome assessors blinded |
|---|---|---|---|---|---|---|
| Rossi, 1983[28] | Unclear | Unclear | No | No | Unclear | Unclear |
| Yusuf, 1983[29] | Unclear | No | No | No | Unclear | Unclear |
| ISIS-1, 1986[1] | Unclear | Yes | No | No | Unclear | Unclear |
| Hjalmarson Å, 1981[30] | Unclear | No | Yes | Yes | Unclear | Unclear |
| MIAMI, 1985[27] | Yes | No | Yes | Yes | Unclear | Unclear |
| Salathia, 1985[31] | Unclear | No | Yes | Yes | Unclear | Unclear |
| Murray, 1986[32] | Unclear | Unclear | Yes | Unclear | Unclear | Unclear |
| Olsson, 1986[33] | Unclear | Unclear | Yes | Yes | Unclear | Unclear |

### 1. Atenolol

The effect of atenolol on ventricular fibrillation following myocardial infarction was examined using data from three studies, shown in Table 5. Only one study showed a significant reduction in ventricular fibrillation.[1] When the three studies were summated together, the weighted absolute risk reduction was 0.3%, which was not significantly different from zero (p=0.232). On the basis of the event rate in the control groups, and the associated small reduction in risk with atenolol, the number of patients needed to be recruited to achieve a significant effect with atenolol at the 5% level and with a power of ≥80% would have been in excess of 42350 per treatment arm.

**Table 5. The effect of atenolol versus placebo on ventricular fibrillation post myocardial infarction**

| Study | Number of patients with VF/ Number on atenolol | Number of patients with VF/ Number of controls | Follow-up | Absolute risk reduction (%) | p value | 95% confidence intervals | 99% confidence intervals |
|---|---|---|---|---|---|---|---|
| Rossi, 1983[28] | 1/95 | 5/87 | 10 days | 4.69 | 0.11 | 0.18 (0.01-1.32) | 0.18 (0.001-2.18) |
| Yusuf, 1983[29] | 3/244 | 13/233 | 10 days | 4.35 | 0.01 | 0.21 (0.05-0.73) | 0.21 (0.03-1.00) |
| ISIS-1, 1986[1] | 189/8037 | 198/7990 | In hospital | 0.13 | 0.64 | 0.97 (0.88-1.08) | 0.97 (0.85-1.11) |
| Total events | 193/8386 (2.3%) | 216/8310 (2.6%) | | 0.30* | 0.23 | 0.94 (0.85-1.04) | 0.94 (0.82-1.08) |

* weighted risk reduction using a weighting factor based on individual trial sizes

Test for heterogeneity: $\chi^2$ 14.27 (6df), p=0.027

### 2. Metoprolol

Similar to the findings with atenolol, the effects of metoprolol in preventing ventricular fibrillation following MI did not achieve significance (p=0.125) (Tables 6). Only one study showed a significant decrease in in-hospital ventricular fibrillation.[30] The weighted absolute risk reductions with metoprolol was 0.5%. Again, the number of patients per

treatment arm, to achieve a significant effect with metoprolol at the 5% level and with a power of ≥80%, would be in excess of 12410.

**Table 6. The effect of metoprolol versus placebo on ventricular fibrillation post myocardial infarction**

| Study | Number of patients with events/ Number on metoprolol | Number patients with events/ Number of controls | Follow-up | Absolute risk reduction (%) | p value | 95% confidence intervals | 99% confidence intervals |
|---|---|---|---|---|---|---|---|
| Hjalmarson Å (Götenborg Metoprolol Trial), 1981[30] | 6/698 | 17/697 | 1 week | 1.58 | 0.02 | 0.35 (0.13-0.91) | 0.35 (0.09-1.16) |
| MIAMI, 1985[27] | 48/2877 | 52/2901 | 1 week | 0.12 | 0.76 | 0.96 (0.79-1.18) | 0.96 (0.74-1.26) |
| Salathia, 1985[131] | 10/250 | 13/224 | In hospital | 1.80 | 0.40 | 0.68 (0.29-1.57) | 0.68 (0.21-2.08) |
| *Murray, 1986[32] | 0/60 | 3/66 | 15 days | 4.55 | 0.25 | 0.00 (0.00-1.87) | 0 (0-3.98) |
| †Olsson (Stockholm Metoprololol Trial), 1986[33] | 5/154 | 4/147 | In CCU | -0.53¶ | 1.000 | 1.20 (0.32-4.81) | 1.20 (0.19-8.34) |
| Total for all studies | 69/4039 (1.7%) | 89/4035(2.2%) | | 0.50** | 0.13 | 0.87 (0.73-1.04) | 0.87 (0.69-1.10) |

*VF requiring defibrillation, †VF in CCU, ¶ absolute risk increase

** weighted risk reduction using a weighting factor based on individual trial sizes

Test for heterogeneity: $\chi^2$ 33.58 (12df), p=0.0008

Analysis of the individual studies included in tables 5 and 6 showed significant inter-study variability, with Pearson Chi-squared values of 14.27 (6 df), p=0.027 and 33.58 (12 df), p=0.0008 for tables 5 and 6 respectively.

## Discussion

There are three theoretical pathophysiological mechanisms which could affect the cardioprotective efficacy of atenolol. These include myocardial ischaemic protection, precipitation of pulmonary oedema or cardiogenic shock and cardiac arrhythmic protection. However, atenolol has been shown to decrease the total ischaemic burden[34] in patients with proven coronary artery disease; and it has not been shown to significantly increase pulmonary oedema when administered following acute MI.[1]

Beta-blockers are protective against sudden arrhythmic death following MI.[35-37] The latter accounts for between 22 and 52% of post MI cardiac deaths.[36 37] It is well recognised that the anti-arrhythmic activity of beta-blockers is multifactorial. All beta-blockers (including atenolol) inhibit the spontaneous depolarisation (phase IV) of the sino-atrial node cells and decrease inward calcium flow (by decreasing cyclic AMP).[38-40] Hence, minimising the deleterious effects of tachycardia, ischaemia and increased myocyte cyclic AMP, may prevent the initiation of ventricular arrhythmias.[38-40]

As a group we know that beta-blockers reduce the incidence of sudden arrhythmic death; however the combination of hydrophilicity and cardioselectivity (as is characteristic of atenolol) is theoretically disadvantageous. The beta-blockers with the greatest efficacy in decreasing sudden arrhythmic death following MI and/ or CHF are all lipophilic; including timolol, propranolol, metoprolol, bisoprolol and carvedilol.[9, 41]

The physiochemical properties of atenolol may reduce it's efficacy in preventing life-threatening arrhythmias and sudden death, and so explain the recently reported difference in cardiac outcomes when atenolol is compared with other beta-blockers.[5, 6] In an animal model, ventricular fibrillation was found to be significantly more frequent in the atenolol (as opposed to the metoprolol) group, despite similar heart rates and myocardial ischaemia with coronary artery occlusion. The metoprolol group had similar plasma and cerebrospinal fluid (CSF) metoprolol concentrations compared with the significantly lower CSF to plasma concentration of atenolol.[42] Similarly, administering L-propranolol into the CSF prolonged the time to onset of ventricular fibrillation in an animal model of myocardial coronary artery occlusion.[43] It was proposed that during excitatory states a central action of metoprolol attenuates vagal withdrawal, which significantly decreases ventricular fibrillation in comparison to atenolol, during myocardial ischaemia.[42]

Unopposed beta-2 adrenergic receptor stimulation increases QT dispersion, which in turn increases the heterogeneity of ventricular repolarisation and thereby increases the risk of ventricular arrhythmias in susceptible individuals.[44] Beta-2 stimulation may also increase the calcium influx associated with ventricular fibrillation during myocardial ischaemia, precipitating ventricular fibrillation.[45] Beta-2 agonism may explain arrhythmias reported in patients with asthma and chronic obstructive pulmonary disease.[46]

Despite the theoretical possibility that the combination of a hydrophilic, cardioselective beta-blocker (such as atenolol) may be less effective at suppressing life-threatening ventricular arrhythmias in comparison to other beta-blockers, this review fails to show a difference in the efficacy of atenolol and metoprolol in preventing ventricular fibrillation following MI despite contrasting ancillary properties (Table 1).

### Criticisms of this systematic review

There are four potential criticisms of this review. Firstly, the autonomic discharge associated with acute MI is an early feature (usually within the first 24 hours).[47] It is during this early time period following MI when patients are theoretically most likely to benefit from lipophilic beta-blockade. However, in this review not all the studies recruited patients within 24 hours of a MI, and the incidence of ventricular fibrillation recorded was for the entire in-hospital admission. If ancillary properties are important in preventing ventricular fibrillation, then one would expect it to be most efficacious during the acute period associated with autonomic release. Interestingly, the recently published Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) which recruited over 45 000 patients showed no significant decrease in ventricular fibrillation within the first day following MI despite the use of a theoretically advantageous lipophilic beta-blocker, metoprolol.[37] The mean entry time into this study following MI was 10.3 (6.7) hours.[37] Indeed, the efficacy of metoprolol in prevention of ventricular fibrillation only appeared after two days.[37] This study casts serious doubt on any additional anti-arrhythmic activity of a lipophilic beta-blocker.[37]

Secondly, the heterogeneity of the systematic review may cast doubt on the findings presented. As evidence in tables 5 and 6, there is considerable heterogeneity in the differing efficacies of both beta-blockers over control treatments; the greater heterogeneity within the results for metoprolol may be

due to the differences in endpoints of the individual included studies, as well as the variable sample sizes and observed absolute risk reductions. It is difficult to suggest how any future analysis might overcome these factors. However, COMMIT found an in-hospital incidence of ventricular fibrillation in the control group of 3.0% with an absolute risk reduction of 0.5% after administration of metoprolol.[37] We found a control incidence of 2.2% with an absolute risk reduction of 0.5% with metoprolol (Table 6).

Thirdly, one may criticise the time period of this review. However, by minimising other confounders by using this approach, one is more likely to identify the cardioprotective efficacy of the beta-blocker investigated. This is crucial as it took nearly 20 years to identify the inefficacy atenolol in the management of hypertension,[4] a scenario which should not be repeated in the peri-operative management of patients with coronary disease.

Finally, the medical management of MI has changed substantially since the 1980's, which may further diminish the theoretical benefit of lipophilic beta-blockers in preventing ventricular fibrillation, which is borne out by the COMMIT finding of no significant reduction in ventricular fibrillation within the first two days following MI.[37]

## Conclusion

Although, atenolol has no survival benefit following MI in medical patients[5,6] it is possibly cardioprotective in the peri-operative period.[18] The findings of this limited systematic review and COMMIT[37] suggest that metoprolol may prevent ventricular fibrillation following MI in five patients out of a 1000, and atenolol may prevent ventricular fibrillation in 3 patients out of a 1000. In comparison, the NNT to prevent postoperative myocardial ischaemia in the peri-operative beta-blocker trials which report major cardiovascular complications is 13.[18-20, 23-25, 48,49] Clearly, the prevention of peri-operative myocardial ischaemia is clinically more important than whether a beta-blocker is lipo or hydrophilic. In addition, Raby et al's study[24] is an important pointer to future studies, confirming that goal-directed control of heart rate appears to be successful in preventing cardiac events in high risk patients.

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