Early intravenous then oral metoprolol in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial

*COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group**

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Summary

Background Despite previous randomised trials of early β-blocker therapy in the emergency treatment of myocardial infarction (MI), uncertainty has persisted about the value of adding it to current standard interventions (eg, aspirin and fibrinolytic therapy), and the balance of potential benefits and hazards is still unclear in high-risk patients.

Methods 45 852 patients admitted to 1250 hospitals within 24 h of suspected acute MI onset were randomly allocated metoprolol (up to 15 mg intravenous then 200 mg oral daily; n=22 929) or matching placebo (n=22 923). 93% had ST-segment elevation or bundle branch block, and 7% had ST-segment depression. Treatment was to continue until discharge or up to 4 weeks in hospital (mean 15 days in survivors) and 89% completed it. The two prespecified co-primary outcomes were: (1) composite of death, reinfarction, or cardiac arrest; and (2) death from any cause during the scheduled treatment period. Comparisons were by intention to treat, and used the log-rank method. This study is registered with ClinicalTrials.gov, number NCT 00222573.

Findings Neither of the co-primary outcomes was significantly reduced by allocation to metoprolol. For death, reinfarction, or cardiac arrest, 2166 (9·4%) patients allocated metoprolol had at least one such event compared with 2261 (9·9%) allocated placebo (odds ratio [OR] 0·96, 95% CI 0·90–1·01; p=0·1). For death alone, there were 1774 (7·7%) deaths in the metoprolol group versus 1797 (7·8%) in the placebo group (OR 0·99, 0·92–1·05; p=0·69). Allocation to metoprolol was associated with five fewer people having reinfarction (464 [2·0%] metoprolol *vs* 568 [2·5%] placebo; OR 0·82, 0·72–0·92; p=0·001) and five fewer having ventricular fibrillation (581 [2·5%] *vs* 698 [3·0%]; OR 0·83, 0·75–0·93; p=0·001) per 1000 treated. Overall, these reductions were counterbalanced by 11 more per 1000 developing cardiogenic shock (1141 [5·0%] *vs* 885 [3·9%]; OR 1·30, 1·19–1·41; p<0·00001). This excess of cardiogenic shock was mainly during days 0–1 after admission, whereas the reductions in reinfarction and ventricular fibrillation emerged more gradually. Consequently, the overall effect on death, reinfarction, arrest, or shock was significantly adverse during days 0–1 and significantly beneficial thereafter. There was substantial net hazard in haemodynamically unstable patients, and moderate net benefit in those who were relatively stable (particularly after days 0–1).

Interpretation The use of early β-blocker therapy in acute MI reduces the risks of reinfarction and ventricular fibrillation, but increases the risk of cardiogenic shock, especially during the first day or so after admission. Consequently, it might generally be prudent to consider starting β-blocker therapy in hospital only when the haemodynamic condition after MI has stabilised.

Introduction

β-blocker therapy is of proven value in the treatment of arrhythmias and hypertension, as well as for long-term secondary prevention after unstable angina and myocardial infarction (MI).[1–4] More recently, despite having previously been considered contraindicated, the use of β blockers has been shown to be beneficial in chronic heart failure.[5,6] The emergency treatment of suspected acute MI with intravenous then oral β-blocker therapy has also been studied in more than two dozen randomised trials.[1,7–9] Overall, those trials included more than 27 000 patients, but nearly all were done before fibrinolytic and antiplatelet therapy had become routine, and they mainly involved fairly low-risk patients (average control mortality was 4%). Collectively, though not separately, their results indicated that this treatment was safe and moderately effective in such low-risk patients, preventing six (SE 3) deaths per 1000.[9] Moreover, results of retrospective analyses suggested that there might be somewhat greater benefits in higher-risk patients with ST-segment elevation[9] or congestive heart failure.[7,8] Despite these findings, however, substantial uncertainty has persisted about the value of adding early β-blocker therapy to current standard interventions (eg, aspirin and fibrinolytic therapy) in acute MI,[10,11] and its use is limited and varies widely.[12–14]

In the previous trials, mortality during the first day or two after suspected acute MI seemed to be reduced by about a quarter with early β-blocker therapy,[9] and this has been tentatively attributed to the prevention of life-threatening arrhythmias and cardiac rupture.[9,15] By contrast, fibrinolytic therapy has been shown to be associated with a small increase in mortality during this early period, perhaps at least in part due to an excess of cardiac rupture.[16] Consequently, use of early β-blocker therapy in conjunction with fibrinolytic therapy might be

particularly effective.[10,15–17] A few trials have attempted to assess this combination, but none was big enough to be reliably informative.[17–19] Moreover, concerns have been raised about the potential hazards of intravenous rather than oral β-blocker therapy in acute MI.[11] The aim of this study was to assess the balance of risks and benefits of adding early intravenous then oral metoprolol to current standard therapies in a wide range of patients.

Methods

COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial; also Second Chinese Cardiac Study [CCS-2]) is a randomised placebo-controlled trial with a 2×2 factorial design, which separately assessed the efficacy and safety of early β-blocker therapy (intravenous then oral metoprolol) and of antiplatelet therapy (adding clopidogrel to aspirin) in suspected acute MI. Details of the study objectives, design, and methods have been reported previously[20] and in the accompanying paper,[21] and are summarised below.

Patients

Recruitment took place between August, 1999, and February, 2005. Patients who presented with ST elevation, left-bundle branch block, or ST depression within 24 h of the onset of the symptoms of suspected acute MI were potentially eligible for the study, provided that their responsible physician did not consider them to have clear indications for, or contraindications to, any of the study treatments. Patients scheduled for primary percutaneous coronary intervention (PCI) were to be excluded because the combined use of aspirin plus clopidogrel (or ticlopidine) was likely to be considered indicated.[20] Otherwise, the exact reasons for excluding patients were determined by the responsible physician based on general guidance in the protocol, and included: either small likelihood of worthwhile benefit (eg, other life-threatening disease or unconvincing history of MI) or high risk of adverse effects with the study treatments. Criteria for a high risk of adverse effects with metoprolol would generally have included persistently low blood pressure (eg, systolic blood pressure below 100 mm Hg), or low heart rate (eg, below 50 bpm), heart block, or cardiogenic shock.[20] By contrast to some of the previous trials,[7] evidence of moderate heart failure (Killip II or III) was not an exclusion criteria.

Written or witnessed oral informed consent was obtained from potentially eligible patients, and no payments to patients were made for participation. Before the start of the study, approval was obtained from the Chinese Ministry of Health, the Chinese State Food and Drug Administration, and the central ethics committee of the Chinese Academy of Medical Sciences. All collaborating hospitals also obtained approval from a local ethics committee or institutional research review board. Collaborating hospitals were reimbursed only nominally for recruitment of eligible patients.

Procedures

Random allocation of the study treatments involved sequentially-numbered sealed treatment packs prepared centrally.[20] Every pack contained three metoprolol or placebo ampoules for intravenous injection and a 4-week calendar-pack of metoprolol or placebo tablets (along with a 4-week calendar pack of aspirin plus clopidogrel or placebo tablets[20]). The first intravenous injection of 5 mg metoprolol or matching placebo was to be given immediately over about 2–3 min. About 2–3 min later, if the heart rate was above 50 bpm and systolic blood pressure above 90 mm Hg, the second ampoule was to be injected; and similarly for the third ampoule (otherwise part or all of the second and third intravenous treatment could be avoided). 15 min after these intravenous doses, a 50 mg metoprolol or placebo tablet was to be given, and repeated every 6 h during days 0–1. From day 2 onwards, a 200 mg controlled-release metoprolol or placebo tablet was to be given once daily for up to 4 weeks (or, if earlier, until hospital discharge or death), unless some definite contraindication was thought to have arisen. All other aspects of the patients' management were entirely at the discretion of their responsible doctors, except that non-study β-blocker (and non-study antiplatelet) therapy[20] was to be avoided during the scheduled treatment period unless it was believed that some strong indication had developed (eg, uncontrolled chest pain or hypertension). For patients receiving fibrinolytic therapy, treatment was generally started before randomisation in case some clear contraindication developed (eg, hypotension).

At the first discharge from hospital or at day 28 (whichever came first), a single-sided follow-up form was to be completed and returned to the national coordinating centre in Beijing. This form described treatment compliance, use of other therapies, possible side-effects, major clinical events, and, if dead before discharge, the probable main cause of death. After the first hospital discharge (or day 28), no further follow-up was sought. Post-discharge use of aspirin, β-blocker, and other established therapies was encouraged but not monitored.

The two prespecified co-primary outcomes for assessment of the efficacy of metoprolol were: the composite of death, reinfarction, or cardiac arrest (including ventricular fibrillation); and death from any cause during the scheduled treatment period (ie, until first discharge or day 28). Secondary endpoints were reinfarction, ventricular fibrillation, other cardiac arrest, cardiogenic shock, and related conditions. All outcomes were reviewed and, if necessary, additional information was sought to allow adjudication (without knowledge of the study treatment allocation) by clinical staff in the coordinating centres.[21] Confirmation of cardiogenic shock required evidence of: systolic blood pressure of less than 80 mm Hg for at least 30 min and use of vasopressors; and clinical evidence of end-organ hypoperfusion (eg, thready pulse, cold clammy skin,

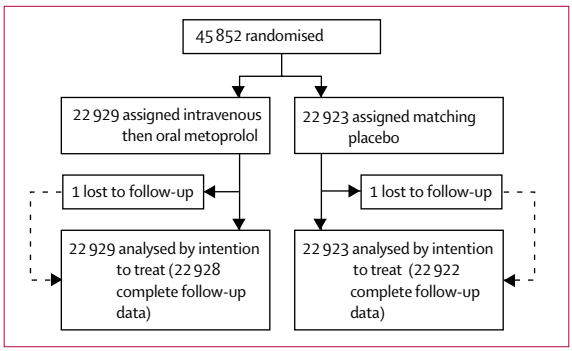


Figure 1: **Trial profile**

	Metoprolol (n=22 929)	Placebo (n=22 923)
Age at entry (years)		
<60	9459 (41·3%)	9628 (42·0%)
60–69	7489 (32·7%)	7342 (32·0%)
⩾70	5981 (26·1%)	5953 (26·0%)
Mean (SD)	61·4 (11·8)	61·3 (11·8)
Sex		
Female	6431 (28·0%)	6328 (27·6%)
Time since onset (h)		
<6	7771 (33·9%)	7681 (33·5%)
6 to <13	7500 (32·7%)	7572 (33·0%)
13–24	7658 (33·4%)	7670 (33·5%)
Mean (SD)	10·3 (6·7)	10·3 (6·7)
Systolic blood pressure (mm Hg)		
<120	7724 (33·7%)	7675 (33·5%)
120–139	8111 (35·4%)	8089 (35·3%)
140–159	4443 (19·4%)	4577 (20·0%)
⩾160	2651 (11·6%)	2582 (11·3%)
Mean (SD)	128·2 (22·6)	128·2 (22·5)
Heart rate (bpm)		
<70	5179 (22·6%)	4958 (21·6%)
70–89	11 076 (48·3%)	11 186 (48·8%)
90–109	5080 (22·2%)	5129 (22·4%)
⩾110	1594 (7·0%)	1650 (7·2%)
Mean (SD)	82·0 (17·3)	82·3 (17·1)
ECG abnormality at entry		
ST elevation	19 868 (86·7%)	19 887 (86·8%)
Bundle branch block	1431 (6·2%)	1497 (6·5%)
ST depression (without ST elevation)	1630 (7·1%)	1539 (6·7%)
Killip class		
I	17 276 (75·3%)	17 327 (75·6%)
II	4573 (19·9%)	4532 (19·8%)
III	1080 (4·7%)	1064 (4·6%)
Previous disease and drug use		
Previous MI	1925 (8·4%)	1893 (8·3%)
Previous hypertension	9948 (43·4%)	9890 (43·1%)
Aspirin before admission	4219 (18·4%)	4225 (18·4%)
β blocker before admission	1484 (6·5%)	1506 (6·6%)
Fibrinolytic agent before randomisation	11 407 (49·7%)	11 387 (49·7%)
Non-trial treatment during hospital stay		
Non-trial β blocker	1395 (6·1%)	3607 (15·7%)
Fibrinolytic agents before or after entry	12 458 (54·3%)	12 509 (54·6%)
Anticoagulant	17 051 (74·4%)	17 128 (74·7%)
Antiarrhythmic	5034 (22·0%)	5209 (22·7%)
ACE inhibitor	15 397 (67·2%)	15 890 (69·3%)
Nitrate (oral or intravenous)	21 584 (94·1%)	21 621 (94·3%)
Diuretic	5553 (24·2%)	5135 (22·4%)
Calcium antagonist	2508 (10·9%)	2898 (12·6%)

Data are number (%) unless otherwise indicated.

Table 1: **Baseline characteristics and concomitant therapies in hospital**

peripheral cyanosis, oliguria). Irrespective of the diagnostic criteria, any unrefuted reported event was included in the analyses. There was extensive central monitoring of study data and on-site audits throughout the trial.[21] Doctors (and patients) were not asked whether they could guess the treatment allocation, but there must have been some occasions in which a rapid reduction in blood pressure correctly indicated to the doctor that active drug was being given.

The main prespecified subsidiary comparisons were to be of the effects of metoprolol on the co-primary outcomes by days of event in hospital. Others were of those outcomes in certain subgroups (eg, age, sex, delay from symptom onset, use of fibrinolytic therapy, Killip class, systolic blood pressure, heart rate). For the many further analyses that might be undertaken, due allowance was to be made for their exploratory (and, perhaps, data-dependent) nature. Because allocation to metoprolol decreased the risk of reinfarction and ventricular fibrillation but increased the risk of cardiogenic shock (see Results), retrospective analyses of the net effects of metoprolol on death, reinfarction, cardiac arrest, or cardiogenic shock were done in various circumstances. In addition, relevant baseline variables (age, sex, Killip class, time from symptom onset, ECG abnormalities, blood pressure, heart rate, previous hypertension) were used retrospectively to categorise patients into three shock risk categories (low, medium, or high).

Statistical analysis

Based on the results of a previous study in China,[22] the placebo-group event rate was anticipated to be about 14% (10% death plus 4% non-fatal reinfarction or arrest). During the study, however, the event rate in both treatment groups combined was only 10% (8% death plus 2% non-fatal). Hence, to have at least 95% statistical power to detect a reduction of one tenth with a two-sided p value of 0·05, at least 45 000 patients needed to be recruited. Interim analyses of efficacy and safety were done yearly for the independent data monitoring committee, although the study continued until its scheduled completion in February, 2005.[21]

The data analysis plan was prespecified in the original protocol[20] and in amendments (http://www.commit-ccs2.org) made before the results were available. Analyses involved comparisons based on the randomly allocated treatments (ie, intention-to-treat[23]) of outcomes occurring after randomisation and before first discharge from hospital (or day 28, if earlier). The time-to-event analyses are based on the first relevant event during the scheduled treatment period in hospital.[21] The main effects of active treatment might affect whether or not a suspected infarct was eventually confirmed; side-effects of active treatment sufficiently severe to cause non-compliance might be particularly likely in more severely ill patients; and deterioration of the patient's condition

would often cause the trial treatment to be interrupted. Hence, analyses restricted to those whose infarct was eventually confirmed or those fully compliant with study treatment would be inappropriate, and could introduce major biases into the present metoprolol analyses (and minor biases into the accompanying clopidogrel analyses[21]). Intention-to-treat analyses avoid all such biases.[23]

This study is registered with ClinicalTrials.gov, number NCT00222573.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The writing committee had final responsibility for the decision to submit for publication.

Results

45 852 patients with suspected acute MI were randomised from 1250 Chinese hospitals to receive either intravenous then oral metoprolol (n=22 929) or matching placebo (n=22 923) for up to 28 days in hospital.[21] Follow-up to first discharge or day 28 was available for all but two patients (figure 1). At discharge, the diagnosis was confirmed as MI in 95·8% (n=21 993 metoprolol and n=21 955 placebo) of randomised patients, possible MI in 1·8% (405 and 409), unstable angina in 1·3% (294 and 302), and other conditions in 1·1% (236 and 256). Irrespective of the final diagnosis, all randomised patients were included in intention-to-treat comparisons of outcome.

Patients' characteristics

The large sample size ensured good balance between the two treatment groups with respect to baseline characteristics (table 1). Mean age was 61 years, with 11 934 (26%) patients aged 70 years or older, and 12 759 (28%) women enrolled. Mean time from symptom onset was 10 h, with 15 452 (34%) patients randomised within 6 h. The presenting ECG showed ST elevation in 39 755 (87%) patients and bundle branch block in 2928 (6%), with the remainder having ST depression alone. Heart failure (Killip II or III) was present at entry in 11 249 (24%) patients, 15 399 (34%) had systolic blood pressure lower than 120 mm Hg, and 3244 (7%) had heart rate over 110 bpm. Previous MI was recorded in 3818 (8%) patients and hypertension in 19 838 (43%). β-blocker therapy had been used before hospital admission by 2990 (7%) patients. Fibrinolytic therapy (mainly urokinase) had been received by 22 794 (50%) patients just before randomisation, and by a total of 24 967 (54%) at some time before or after randomisation (68% in those presenting within 12 h with ST-elevation). During the hospital stay, there were no significant differences between the treatment groups in the use of fibrinolytic, anticoagulant (mainly heparin), or nitrate therapy. But somewhat fewer metoprolol-allocated patients received non-study β blocker (6·1% metoprolol *vs* 15·7% placebo; p<0·0001), antiarrhythmic agents (22·0% *vs* 22·7%; p<0·05), ACE inhibitors (67·2% *vs* 69·3%; p<0·0001), and calcium antagonists (10·9% *vs* 12·6%, p<0·0001), and somewhat more received diuretics (24·2% *vs* 22·4%; p<0·0001).

About 99% of patients in both groups started the intravenous metoprolol or placebo treatment, and all three injections were received by 90% of those allocated

	Metoprolol (n=22 929)	Placebo (n=22 923)
Intravenous medication		
Not started at all	335 (1·5%)	308 (1·3%)
One or part of one dose given	916 (4·0%)	303 (1·3%)
>1 and <3 doses completed	955 (4·2%)	269 (1·2%)
Some injection given, amount unknown	32 (0·1%)	24 (0·1%)
All three doses completed	20 691 (90·2%)	22 019 (96·1%)
Oral medication		
Not started at all	129 (0·6%)	90 (0·4%)
Stopped prematurely	3024 (13·2%)	1836 (8·0%)
Treatment completed	19 776 (86·2%)	20 997 (91·6%)
with temporary dose reduction	72	21
with permanent dose reduction	369	88
with occasional dose skipping	233	139
Mean (SD) scheduled treatment duration (days)*	14·8 (7·9)	15·0 (7·8)

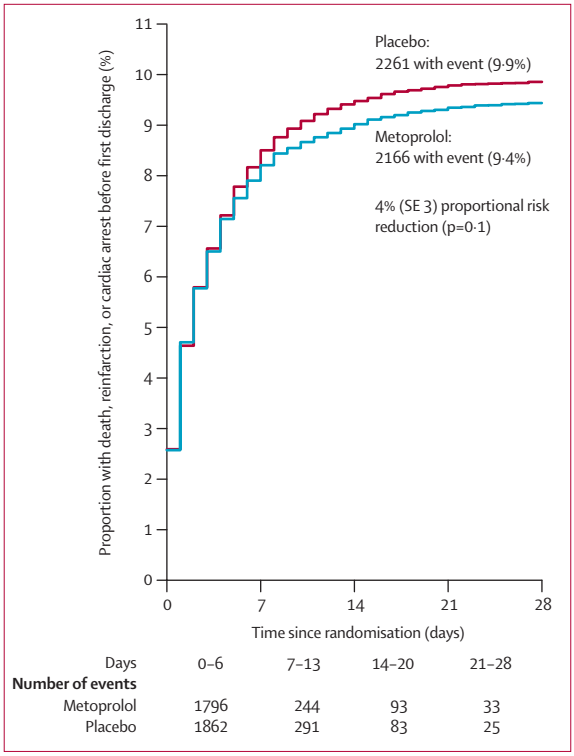
Data are number (%) unless otherwise indicated. *Restricted to those discharged alive before day 28, or still alive and not discharged by day 28.

Table 2: **Compliance by allocated treatment in hospital**

	Metoprolol (n=22 929)	Placebo (n=22 923)	Odds ratio (95% CI)	Absolute difference per 1000 (SE)	p
Co-primary outcomes					
Composite*	2166 (9·4%)	2261 (9·9%)	0·96 (0·90–1·01)	−4·2 (2·8)	0·10
Death	1774 (7·7%)	1797 (7·8%)	0·99 (0·92–1·05)	−1·0 (2·6)	0·69
Death, by recorded cause					
Arrhythmia	388 (1·7%)	498 (2·2%)	0·78 (0·68–0·89)	−4·8 (1·3)	0·0002
Shock†	496 (2·2%)	384 (1·7%)	1·29 (1·13–1·47)	4·9 (1·3)	0·0002
Neither	890 (3·9%)	915 (4·0%)	0·97 (0·89–1·07)	−1·1 (1·8)	0·55
Reinfarction					
Any	464 (2·0%)	568 (2·5%)	0·82 (0·72–0·92)	−4·5 (1·4)	0·001
Died, any cause	206 (0·9%)	226 (1·0%)	0·91 (0·75–1·10)	−0·9 (0·9)	0·33
Survived	258 (1·1%)	342 (1·5%)	0·75 (0·64–0·88)	−3·7 (1·1)	0·0005
Ventricular fibrillation‡					
Any	581 (2·5%)	698 (3·0%)	0·83 (0·75–0·93)	−5·1 (1·6)	0·001
Died, any cause	492 (2·1%)	600 (2·6%)	0·82 (0·73–0·92)	−4·7 (1·4)	0·001
Survived	89 (0·4%)	98 (0·4%)	0·91 (0·68–1·21)	−0·4 (0·6)	0·51
Other cardiac arrest§					
Any	685 (3·0%)	632 (2·8%)	1·08 (0·97–1·21)	2·3 (1·6)	0·14
Died, any cause	624 (2·7%)	593 (2·6%)	1·05 (0·94–1·18)	1·3 (1·5)	0·38
Survived	61 (0·3%)	39 (0·2%)	1·55 (1·05–2·30)	1·0 (0·4)	0·03
Cardiogenic shock¶					
Any	1141 (5·0%)	885 (3·9%)	1·30 (1·19–1·41)	11·2 (1·9)	<0·0001
Died, any cause	755 (3·3%)	628 (2·7%)	1·20 (1·08–1·34)	5·5 (1·6)	0·0006
Survived	386 (1·7%)	257 (1·1%)	1·50 (1·28–1·75)	5·6 (1·1)	<0·0001
Death, reinfarction, cardiac arrest, or shock	2501 (10·9%)	2465 (10·8%)	1·02 (0·96–1·08)	1·5 (2·5)	0·54

Data are number (%) unless otherwise indicated. *Death, reinfarction, ventricular fibrillation, or other arrest (irrespective of any mention of shock). †Excludes 185 (87 metoprolol *vs* 98 placebo) deaths with both arrhythmia and shock recorded as causes. ‡Includes ventricular fibrillation as recorded or any death with arrhythmia recorded as a cause. §Includes other arrest as recorded or any death with asystole recorded as a cause (excluding any with ventricular fibrillation or death with arrhythmia as a cause). ¶Including cardiogenic shock as recorded or any death from shock (irrespective of whether other causes were also recorded).

Table 3: **Effects of metoprolol on main clinical events during scheduled treatment period in hospital**



Days	0–6	7–13	14–20	21–28
Number of events				
Metoprolol	1796	244	93	33
Placebo	1862	291	83	25

Figure 2: **Effects of metoprolol allocation on death, reinfarction, or cardiac arrest before first discharge from hospital**
Time-to-event analyses based on first relevant event during scheduled treatment period. Mean treatment duration in survivors was 14·9 days. Flatness of right-hand ends of graph is because events after discharge were not included.

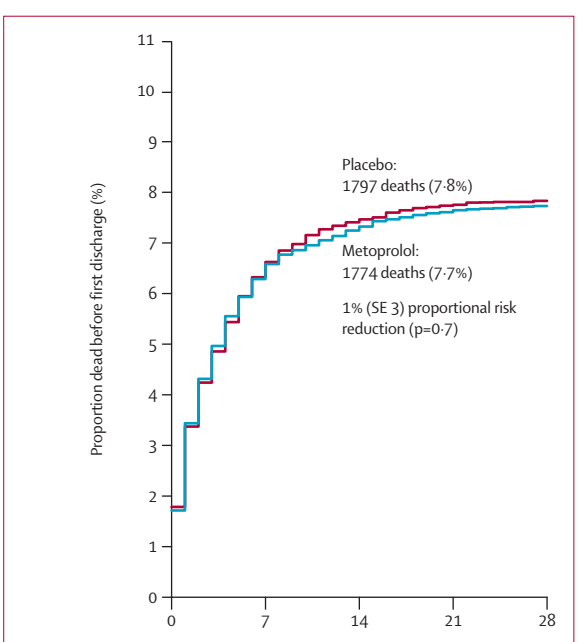
metoprolol and 96% of those allocated placebo (table 2). The main reasons for not receiving all three injections were persistent hypotension alone (3·2% metoprolol *vs* 1·1% placebo), bradycardia alone (2·9% *vs* 0·7%), or both (1·0% *vs* 0·2%). For the oral metoprolol or placebo treatment, 86·2% metoprolol-allocated versus 91·6% placebo-allocated patients completed the scheduled treatment, with the mean time to first discharge or day 28 in survivors in both groups being about 15 days (quartiles: 9, 14, and 21 days: table 2). As with the intravenous injections, the main reasons for stopping prematurely were persistent hypotension alone (2·7% *vs* 1·3%), bradycardia alone (3·1% *vs* 0·8%), or both (0·8% *vs* 0·2%). Treatment compliance was strongly related to age, systolic blood pressure, heart rate, and Killip class at entry, and was similar to that in previous trials of such regimens in European and American populations (especially in similar types of patients).[7]

Primary efficacy and safety outcomes

Neither of the co-primary outcomes was significantly reduced during the scheduled treatment period by allocation to intravenous then oral metoprolol. For the primary composite outcome of death, reinfarction, or cardiac arrest, 2166 (9·4%) patients had at least one such event among the 22 929 allocated metoprolol compared with 2261 (9·9%) among the 22 923 allocated matching placebo, which corresponds to an odds ratio of 0·96 (95% CI 0·90–1·01; p=0·10: table 3 and figure 2). For the co-primary outcome of death alone, there were 1774 (7·7%) deaths in the metoprolol group versus 1797 (7·8%) in the placebo group, corresponding to an odds ratio of 0·99 (0·92–1·05; p=0·69: table 3 and figure 3).

When the attributed causes of death were considered separately (table 3), however, allocation to metoprolol was associated with a highly significant 22% (11–32) proportional reduction in death attributed to arrhythmia (388 [1·7%] metoprolol *vs* 498 [2·2%] placebo; p=0·0002) and, by contrast, with a highly significant 29% (13–47) proportional increase in death attributed to cardiogenic shock (496 [2·2%] *vs* 384 [1·7%]; p=0·0002). On average in the whole study population, the absolute reduction in arrhythmia-related deaths and the absolute increase in shock-related deaths were of similar magnitude. No apparent difference was noted between the two treatment groups in the other attributed causes of death, either individually or in aggregate (890 [3·9%] *vs* 915 [4·0%]; p=0·55).

Allocation to metoprolol produced a highly significant 18% (8–28) proportional reduction in the risk of any (fatal or not) reinfarction during the scheduled treatment period (464 [2·0%] metoprolol *vs* 568 [2·5%] placebo; p=0·001: table 3). Although the proportional reduction seemed to be somewhat greater for non-fatal reinfarction



Days	0–6	7–13	14–20	21–28
Number of events				
Metoprolol	1441	220	83	30
Placebo	1449	249	75	24

Figure 3: **Effects of metoprolol allocation on death before first discharge from hospital**
Conventions as in figure 2.

(25% [SE 7]) than for fatal reinfarction (9% [SE 9]), the difference between these effects was not significant (heterogeneity p=0·13). Metoprolol was also associated with a highly significant 17% (7–25) proportional reduction in the risk of ventricular fibrillation (581 [2·5%] *vs* 698 [3·0%]; p=0·001), but not with any apparent effect on other cardiac arrest (685 [3·0%] *vs* 632 [2·8%]; p=0·14). Overall, allocation to intravenous followed by oral metoprolol for about 2 weeks produced absolute reductions of five (SE 1·4) per 1000 in reinfarction and of five (SE 1·6) per 1000 in ventricular fibrillation. By contrast, it produced a highly significant 30% (19-41) proportional increase in cardiogenic shock (1141 [5·0%] *vs* 885 [3·9%]; p<0·0001), which corresponded on average to an absolute excess of 11 (SE 2) per 1000 treated. Most who developed cardiogenic shock died (66% of metoprolol and 72% of placebo cases), and the excess risk with metoprolol was significantly greater for non-fatal cases (odds ratio 1·50, 1·28–1·75) than for fatal cases (odds ratio 1·20, 1·08–1·34; heterogeneity p=0·02). When the primary composite efficacy outcome of death, reinfarction, or cardiac arrest was considered together with the safety outcome of cardiogenic shock, there was no net difference between the treatment groups in the overall number of patients having any such event (2501 [10·9%] metoprolol *vs* 2465 [10·8%] placebo; p=0·54: table 3).

Other in-hospital outcomes

Allocation to metoprolol was associated with a highly significant 12% (7–18) proportional increase in the numbers of people who developed heart failure, but not shock, requiring treatment (3224 [14·1%] metoprolol *vs* 2902 [12·7%] placebo; p<0·0001: table 4). But few of these episodes of heart failure led to death, and allocation to metoprolol was not associated with a significant excess of fatal episodes (330 [1·4%] vs 359 [1·6%]; p=0·27). In patients who did not develop cardiogenic shock, metoprolol allocation was associated with significantly more persistent hypotension (6·0% *vs* 2·9%; odds ratio 2·06, 1·89–2·25; p<0·0001), with similar proportional increases in cases of hypotension that did (odds ratio 1·87) or did not (odds ratio 2·28) receive inotropic agents. Moreover, there were also significantly more cases of bradycardia reported with metoprolol allocation (5·4% *vs* 2·2%; odds ratio 2·41, 2·19–2·65; p<0·0001). Allocation to metoprolol produced no significant effects on other major outcomes that were to be recorded systematically during the scheduled treatment period, such as: stroke, presumed cardiac rupture, pulmonary embolus, and any major or minor non-cerebral bleeding (table 4).

With respect to outcomes that were not systematically sought, analyses restricted to patients discharged alive did not find any significant difference in the reported incidence of atrial-ventricular block (1·6% *vs* 1·6%: table 4). There was an increase in other voluntarily

	Metoprolol (n=22 929)	Placebo (n=22 923)	Odds ratio (95% CI)	Absolute difference per 1000 (SE)	p
Heart failure (but no shock)					
Any	3224 (14·1%)	2902 (12·7%)	1·12 (1·07–1·18)	14·0 (3·1)	<0·0001
Died, any cause	330 (1·4%)	359 (1·6%)	0·92 (0·79–1·07)	−1·3 (1·2)	0·27
Survived	2894 (12·6%)	2543 (11·1%)	1·15 (1·09–1·21)	15·3 (3·0)	<0·0001
Persistent hypotension (but no shock)					
Any	1374 (6·0%)	668 (2·9%)	2·06 (1·89–2·25)	30·8 (1·9)	<0·0001
With inotrope	792 (3·5%)	421 (1·8%)	1·87 (1·67–2·10)	16·2 (1·5)	<0·0001
Without inotrope	582 (2·5%)	247 (1·1%)	2·28 (1·98–2·61)	14·6 (1·2)	<0·0001
Bradycardia					
Any	1235 (5·4%)	500 (2·2%)	2·41 (2·19–2·65)	32·0 (1·8)	<0·0001
Stroke, by type					
Any	247 (1·1%)	220 (1·0%)	1·12 (0·94–1·35)	1·2 (0·9)	0·21
Ischaemic (or unknown)	191 (0·8%)	167 (0·7%)	1·14 (0·93–1·41)	1·0 (0·8)	0·20
Haemorrhagic	57 (0·2%)	54 (0·2%)	1·06 (0·73–1·53)	0·1 (0·5)	0·78
Presumed cardiac rupture					
Any	200 (0·9%)	233 (1·0%)	0·86 (0·71–1·04)	−1·4 (0·9)	0·11
Pulmonary embolus					
Any	30 (0·1%)	35 (0·2%)	0·86 (0·53–1·39)	−0·2 (0·4)	0·53
Non-cerebral bleeding					
Any	824 (3·6%)	849 (3·7%)	0·97 (0·88–1·07)	−1·1 (1·8)	0·53
Other adverse events in survivors					
Atrial-ventricular block	370 (1·6%)	357 (1·6%)	1·04 (0·90–1·20)	0·6 (1·2)	0·63
Other vascular*	115 (0·5%)	58 (0·3%)	1·94 (1·44–2·61)	2·5 (0·6)	<0·0001
Respiratory†	47 (0·2%)	11 (0·0%)	3·46 (2·07–5·80)	1·6 (0·3)	<0·0001
Other	31 (0·1%)	27 (0·1%)	1·15 (0·69–1·92)	0·2 (0·3)	0·60

Data are number (%) unless otherwise indicated. *Includes mainly sinus arrest or bradycardia, atrial arrhythmia, bundle branch block, or atrial-ventricular junctional escape. †Includes mainly asthma or bronchospasm.

Table 4: **Effects of metoprolol on other clinical events during scheduled treatment period in hospital**

	Metoprolol (n=22 929)	Placebo (n=22 923)	Odds ratio (95% CI)	Absolute difference per 1000 (SE)	p for trend
Death, any cause					
Day 0	393 (1·7%)	409 (1·8%)	0·96 (0·83–1·10)	−0·7 (1·2)	
Day 1	395 (1·7%)	364 (1·6%)	1·09 (0·94–1·25)	1·3 (1·2)	0·77
Day 2+	986 (4·3%)	1024 (4·5%)	0·96 (0·88–1·05)	−1·7 (2·0)	
Reinfarction*					
Day 0	73 (0·3%)	78 (0·3%)	0·94 (0·68–1·29)	−0·2 (0·5)	
Day 1	135 (0·6%)	152 (0·7%)	0·89 (0·70–1·12)	−0·7 (0·7)	0·17
Day 2+	256 (1·1%)	338 (1·5%)	0·76 (0·64–0·89)	−3·6 (1·1)	
Ventricular fibrillation*					
Day 0	181 (0·8%)	218 (1·0%)	0·83 (0·68–1·01)	−1·6 (0·9)	
Day 1	113 (0·5%)	119 (0·5%)	0·95 (0·73–1·23)	−0·3 (0·6)	0·66
Day 2+	287 (1·3%)	361 (1·6%)	0·80 (0·68–0·93)	−3·2 (1·1)	
Other cardiac arrest*					
Day 0	176 (0·8%)	157 (0·7%)	1·12 (0·90–1·39)	0·8 (0·8)	
Day 1	153 (0·7%)	120 (0·5%)	1·28 (1·01–1·62)	1·4 (0·7)	0·28
Day 2+	356 (1·6%)	355 (1·5%)	1·00 (0·87–1·16)	0·0 (1·8)	
Cardiogenic shock*					
Day 0	476 (2·1%)	316 (1·4%)	1·51 (1·31–1·74)	7·0 (1·2)	
Day 1	281 (1·2%)	209 (0·9%)	1·36 (1·13–1·62)	3·1 (0·9)	0·0009
Day 2+	384 (1·7%)	360 (1·6%)	1·07 (0·93–1·24)	1·0 (1·1)	
Any of above					
Day 0	808 (3·5%)	707 (3·1%)	1·15 (1·04–1·27)	4·4 (1·7)	
Day 1	579 (2·5%)	531 (2·3%)	1·10 (0·97–1·24)	2·1 (1·4)	0·0003
Day 2+	1114 (4·9%)	1227 (5·4%)	0·91 (0·84–0·99)	−4·9 (2·2)	
All	2501 (10·9%)	2465 (10·8%)	1·02 (0·96–1·08)	1·5 (2·5)	

Data are number (%) unless otherwise indicated. *Fatal or not (with some overlap between different outcomes, except for ventricular fibrillation and other cardiac arrest).

Table 5: **Effects of metoprolol on main clinical events, by day of first such event**

	Death			Cardiogenic shock			Combined efficacy and safety endpoint*		
	Metoprolol (n=22 929)	Placebo (n=22 923)	Absolute difference per 1000 (SE)	Metoprolol (n=22 929)	Placebo (n=22 923)	Absolute difference per 1000 (SE)	Metoprolol (n=22 929)	Placebo (n=22 923)	Absolute difference per 1000 (SE)
Age (years)									
<60	339 (3·6%)	358 (3·7%)	−1·3 (2·7)	255 (2·7%)	208 (2·2%)	5·4 (2·2)	593 (6·3%)	614 (6·4%)	−1·1 (3·7)
60–69	621 (8·3%)	645 (8·8%)	−4·9 (4·6)	385 (5·1%)	316 (4·3%)	8·4 (3·5)	878 (11·7%)	866 (11·8%)	−0·7 (9·5)
⩾70	814 (13·6%)	794 (13·3%)	2·7 (5·7)	501 (8·4%)	361 (6·1%)	23·1 (4·7)	1030 (17·2%)	985 (16·5%)	6·7 (6·1)
Sex									
Male	1030 (6·2%)	1041 (6·3%)	−0·3 (2·9)	719 (4·4%)	540 (3·3%)	11·0 (2·1)	1551 (9·4%)	1530 (9·2%)	1·8 (2·9)
Female	744 (11·6%)	756 (11·9%)	−3·8 (5·8)	422 (6·6%)	345 (5·5%)	11·1 (4·2)	950 (14·8%)	935 (14·8%)	0·0 (0·5)
Time since onset (h)									
<6	617 (7·9%)	635 (8·3%)	−3·3 (4·4)	404 (5·2%)	328 (4·3%)	9·3 (3·4)	912 (11·7%)	892 (11·6%)	1·2 (4·4)
6 to <13	601 (8·0%)	640 (8·5%)	−4·4 (4·5)	403 (5·4%)	305 (4·0%)	13·5 (3·4)	830 (11·1%)	869 (11·5%)	−4·1 (5·6)
13–24	556 (7·3%)	522 (6·8%)	4·5 (4·1)	334 (4·4%)	252 (3·3%)	10·8 (3·1)	759 (9·9%)	704 (9·2%)	7·3 (4·6)
Systolic blood pressure (mm Hg)									
<120	738 (9·6%)	679 (8·8%)	7·1 (4·5)	601 (7·8%)	418 (5·4%)	23·3 (4·0)	1060 (13·7%)	931 (12·1%)	15·9 (5·2)
120–139	553 (6·8%)	615 (7·6%)	−7·9 (4·1)	332 (4·1%)	302 (3·7%)	3·6 (3·0)	789 (9·7%)	852 (10·5%)	−8·1 (4·9)
140–159	291 (6·5%)	321 (7·0%)	−4·6 (5·2)	139 (3·1%)	117 (2·6%)	5·7 (3·5)	407 (9·2%)	440 (9·6%)	−4·5 (6·1)
⩾160	192 (7·2%)	182 (7·0%)	1·9 (8·0)	69 (2·6%)	48 (1·9%)	7·4 (4·1)	245 (9·2%)	242 (9·4%)	−1·3 (6·4)
Heart rate (bpm)									
<70	224 (4·3%)	204 (4·1%)	2·1 (4·0)	131 (2·5%)	103 (2·1%)	4·5 (3·0)	357 (6·9%)	336 (6·8%)	1·2 (5·2)
70–89	666 (6·0%)	742 (6·6%)	−6·2 (3·2)	413 (3·7%)	313 (2·8%)	9·3 (2·4)	998 (9·0%)	1034 (9·2%)	−2·3 (4·1)
90–109	561 (11·0%)	549 (10·7%)	3·4 (5·7)	367 (7·2%)	288 (5·6%)	16·1 (4·8)	741 (14·6%)	725 (14·1%)	4·5 (5·9)
⩾110	323 (20·3%)	302 (18·3%)	19·6 (13·7)	230 (14·4%)	181 (11·0%)	34·6 (11·5)	405 (25·4%)	370 (22·4%)	29·8 (14·4)
Killip class									
I	1006 (5·8%)	1060 (6·1%)	−2·9 (2·5)	611 (3·5%)	484 (2·8%)	7·4 (1·9)	1506 (8·7%)	1531 (8·8%)	−1·2 (3·3)
II	555 (12·1%)	561 (12·4%)	−2·4 (8·5)	362 (7·9%)	296 (6·5%)	13·8 (5·3)	724 (15·8%)	714 (15·8%)	0·8 (3·3)
III	213 (19·7%)	176 (16·5%)	31·8 (16·5)	168 (15·6%)	105 (9·9%)	56·9 (14·4)	271 (25·1%)	220 (20·7%)	44·2 (17·6)
Fibrinolytic agent given									
Yes	819 (7·2%)	850 (7·5%)	−2·8 (3·4)	542 (4·8%)	458 (4·0%)	7·3 (2·7)	1209 (10·6%)	1239 (10·9%)	−2·8 (4·3)
No	955 (8·3%)	947 (8·2%)	0·8 (3·2)	599 (5·2%)	427 (3·7%)	15·0 (2·7)	1292 (11·2%)	1226 (10·6%)	5·9 (3·8)
Shock risk index†									
Low	650 (4·0%)	720 (4·5%)	−4·3 (2·2)	367 (2·3%)	308 (1·9%)	3·7 (1·6)	1049 (6·5%)	1133 (7·0%)	−5·1 (2·8)
Medium	570 (12·2%)	595 (12·6%)	−4·2 (7·1)	374 (8·0%)	301 (6·4%)	16·2 (5·3)	767 (16·4%)	763 (16·2%)	2·3 (6·2)
High	554 (25·9%)	482 (23·4%)	24·8 (12·7)	400 (18·7%)	276 (13·4%)	52·8 (11·3)	685 (32·0%)	569 (27·6%)	43·7 (13·0)
Overall	1774 (7·7%)	1797 (7·8%)	−1·0 (2·6)	1141 (5·0%)	885 (3·9%)	11·2 (1·9)	2501 (10·9%)	2465 (10·8%)	1·5 (2·5)

Data are number (%) unless otherwise indicated. *Death, reinfarction, ventricular fibrillation, other arrest or cardiogenic shock. †Based on absolute risk of shock for each individual patient calculated from baseline prognostic variables (including age, sex, time delay, Killip class, blood pressure, heart rate, ECG abnormality, previous hypertension, but excluding allocated treatment) with a Cox regression model.[24]

Table 6: **Absolute effects of metoprolol on death alone, cardiogenic shock alone, and combined efficacy and safety endpoint in certain categories of patients**

reported cardiovascular conditions (0·5% *vs* 0·3%; p<0·0001), which mainly involved sinus arrest or bradycardia, atrial arrhythmia, bundle branch block, and atrial-ventricular junctional escape. There was also an increase in the numbers reported to have various respiratory conditions (0·2% *vs* 0·0%; p<0·0001), mainly involving asthma or bronchospasm.

Subsidiary analyses

Overall, as shown above, there were no significant differences between the treatment groups in the co-primary outcomes of death alone or the composite of death, reinfarction, or cardiac arrest. Moreover, in the study population considered as a whole, the absolute reductions of five per 1000 in reinfarction and of five per 1000 in ventricular fibrillation were counterbalanced by the absolute increase of 11 per 1000 in shock. But the risks of these different outcomes differed by time since randomisation and in various subcategories of patient, and so too did the balance of the effects of metoprolol (tables 5 and 6).[24]

No significant effect of allocation to metoprolol was noted on all-cause mortality during any of the prespecified periods of follow-up (table 5). By contrast, a highly significant ten (SE 1·5; p<0·0001) per 1000 excess risk of cardiogenic shock was noted during days 0–1, with little further excess risk of shock subsequently (p=0·0009 for trend in odds ratio between day 0, 1, and 2+). Reductions in the risks of reinfarction and of ventricular fibrillation with metoprolol seemed to emerge more gradually, with no significant difference between the treatment groups during days 0–1 (reinfarction: 0·9% metoprolol *vs* 1·0% placebo; ventricular fibrillation: 1·3% *vs* 1·5%), but with significant benefit during days 2 onwards (reinfarction: 1·1% *vs* 1·5%; ventricular fibrillation: 1·3% *vs* 1·6%; each p<0·01). Consequently, the overall net effect of metoprolol allocation on the combined efficacy and safety outcome of death, reinfarction, arrest, or shock changed from being significantly adverse during days 0–1 to being significantly beneficial during day 2 onwards (p<0·001 for trend in odds ratio).

Allocation to metoprolol did not produce any clearly significant effect on mortality in any of the subcategories of patient considered separately (table 6). But, when baseline data were used to categorise patients according to their risk of developing shock, there was a highly significant trend (p=0·007 for trend) towards hazard with metoprolol in the high-risk group (absolute increase of 24·8 [SE 12·7] deaths per 1000) and benefit elsewhere (absolute decreases of 4·2 [SE 7·1] and of 4·3 [SE 2·2] deaths per 1000 in the medium-risk and low-risk groups, respectively). Allocation to metoprolol produced a consistent 30% proportional increase in the risk of developing cardiogenic shock across the different categories of patients studied (including those randomised in different types of hospital: p=0·13 for heterogeneity; data not shown). But since the probability of developing shock was much higher in some types of control patients than in others, the absolute excess risks of shock with metoprolol allocation were particularly large in certain baseline categories: for example, 23·1 (SE 4·7) per 1000 for those aged 70 years or older at entry; 23·3 (4·0) per 1000 for those presenting with systolic blood pressure below 120 mm Hg; 34·6 (11·5) per 1000 for those presenting with heart rate of more than 110 bpm; and 56·9 (14·4) per 1000 for those in Killip class III (table 6). Consequently, in patients categorised with respect to their risk of developing shock, there was a highly significant trend in the absolute excess risk: 52·8 (SE 11·3) versus 16·2 (5·3) versus 3·7 (1·6) more per 1000 developing shock in high-risk, medium-risk, and low-risk groups, respectively (trend p<0·0001).

For the combined efficacy and safety outcome, allocation to metoprolol was associated with a marked increased risk in high-risk patients and with a tendency for a risk reduction in low-risk patients. In particular, there was an absolute increase of 43·7 (SE 13·0) such events per 1000 patients in the high shock risk group compared with an absolute increase of only 2·3 (6·2) per 1000 in the medium-risk group and a decrease of 5·1 (2·8) per 1000 in the low shock risk group (trend p<0·0001). When the effects of metoprolol allocation on this outcome in these risk groups were considered according to period since randomisation (table 7), there were particularly large relative and absolute excess risks during days 0–1 in patients allocated metoprolol in the high-risk (55·3 [SE 11·8] more per 1000) and medium-risk (11·8 [SE 5·8] more per 1000) groups compared with the low-risk group (2·0 [SE 2·0] fewer per 1000; p<0·0001 for trend). Subsequently, however, the absolute reductions in this combined outcome in these three groups did not differ significantly (heterogeneity p=0·8) from the average benefit of 4·9 (SE 2·2) fewer events per 1000 that was found during days 2 and onwards in the aggregate of all three groups.

	Metoprolol (n=22 929)	Placebo (n=22 923)	Odds ratio (95% CI)	Absolute difference per 1000 (SE)	p for trend
Day 0–1					
Low	509 (3·2%)	543 (3·4%)	0·94 (0·83–1·06)	−2·0 (2·0)	
Medium	424 (9·1%)	372 (7·9%)	1·16 (1·01–1·34)	11·8 (5·8)	<0·0001
High	454 (21·2%)	323 (15·7%)	1·42 (1·23–1·65)	55·3 (11·8)	
Day 2–28					
Low	540 (3·4%)	590 (3·7%)	0·91 (0·81–1·03)	−3·0 (2·0)	
Medium	343 (7·3%)	391 (8·3%)	0·89 (0·77–1·03)	−9·5 (6·1)	0·7
High	231 (10·8%)	246 (11·9%)	0·97 (0·81–1·16)	−11·5 (30·8)	
Day 0–28*					
Low	1049 (6·5%)	1133 (7·0%)	0·93 (0·85–1·01)	−5·1 (2·8)	
Medium	767 (16·4%)	763 (16·2%)	1·02 (0·92–1·13)	2·3 (6·2)	0·0002
High	685 (32·0%)	569 (27·6%)	1·22 (1·09–1·37)	43·7 (13·0)	

Data are number (%) unless otherwise indicated. *Events before day 28 but after first discharge not included.

Table 7: **Effects of metoprolol on combined efficacy (death, reinfarction, ventricular fibrillation, or other arrest) and safety (cardiogenic shock) endpoint by shock index and day of event**

Discussion

This large randomised trial of intravenous then oral β-blocker therapy for the emergency treatment of acute MI involved nearly twice as many patients and more than three times as many deaths as all previous such trials combined. Nevertheless, its results do not show that such treatment significantly reduced in-hospital mortality, either overall or in a wide range of different circumstances (including patients at high or low risk of death). Allocation to the metoprolol regimen studied did produce highly significant 15–20% proportional reductions in the risks of reinfarction and of ventricular fibrillation, which corresponded to an average of about five fewer patients having reinfarction and about five fewer having ventricular fibrillation for every 1000 patients treated for about 2 weeks in hospital. But overall these benefits were counterbalanced by an average of 11 more per 1000 developing cardiogenic shock. Moreover, whereas identification of any particular patient category in which the net benefit of early β-blocker therapy clearly outweighed the net hazard was not possible, there was evidence that patients already at increased risk of developing shock (ie, those with unstable haemodynamic conditions) were disadvantaged by such treatment.

Reinfarction and ventricular fibrillation

The benefits of long-term oral β-blocker therapy in the years after MI are well established.[1–4] In a meta-analysis of 31 randomised trials, involving 25 000 patients with a history of MI, the long-term use of a β blocker reduced the risks of reinfarction and of death by about 20–25% during an average of 2 years of treatment.[25] This effect on overall mortality was attributed mainly to a reduction in sudden cardiac deaths, most of which are caused by arrhythmias (such as ventricular fibrillation).[26–28] Similarly, in a meta-analysis of 28 randomised trials, involving 27 000 patients with suspected acute MI, intravenous then oral β-blocker therapy seemed to reduce the relative risks of reinfarction and cardiac arrest by

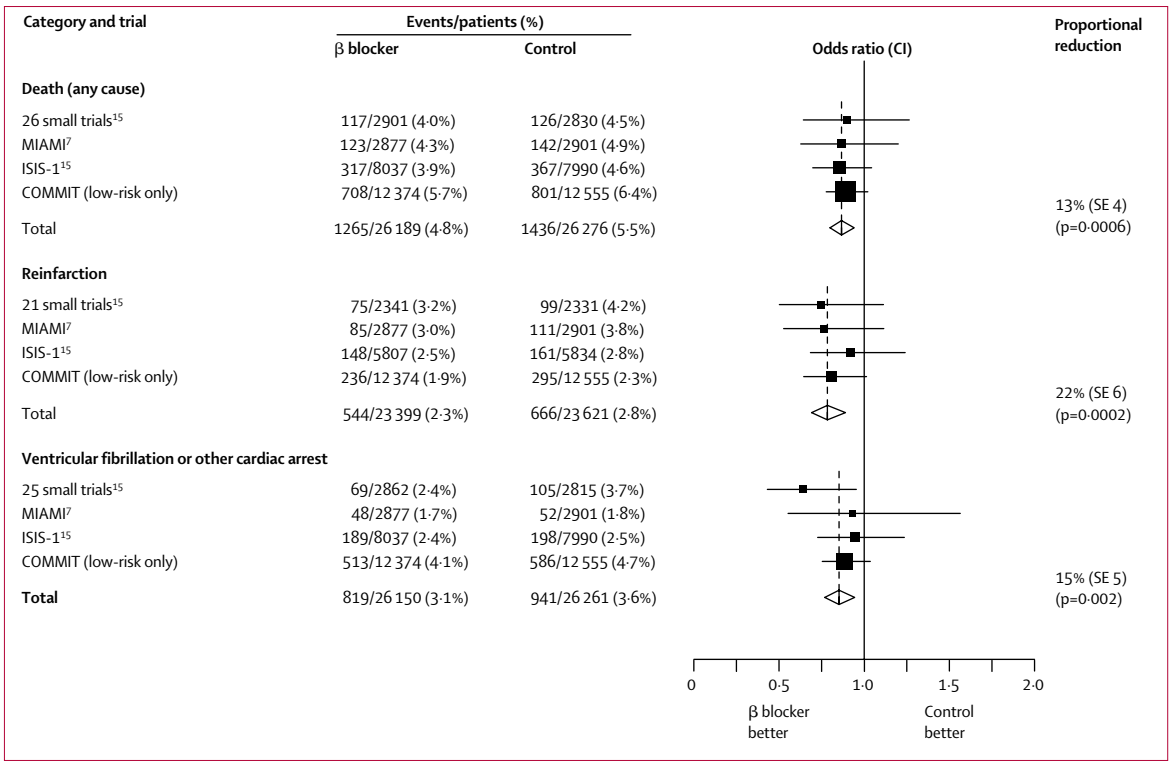


Figure 4: **Meta-analysis of effects of intravenous then oral β-blocker therapy on death, reinfarction, and cardiac arrest during the scheduled treatment periods in 26 small randomised trials, MIAMI, ISIS-1, and the low-risk subset of COMMIT**

For COMMIT, data are included only for patients who presented with systolic blood pressure of more than 105 mm Hg, heart rate of more than 65 bpm, and Killip class I (as in MIAMI[7]). Five small trials included in ISIS-1 report did not have any data on reinfarction. In ISIS-1 trial, data on reinfarction in hospital were available for later three-quarters of study, involving 11 641 patients. Odds ratios (ORs) in each (black squares with area proportional to number of events) comparing outcome in patients allocated β blocker to that in patients allocated control, along with 99% CIs (horizontal line). Overall OR and 95% CI plotted by diamond, with value and significance given alongside. Squares and diamonds are all to left of solid vertical line indicating benefit with β blocker, but this benefit is significant ($p<0·01$) only if the horizontal line ($p<0·01$) or diamond ($p<0·05$) does not overlap the solid vertical line. Broken vertical lines indicate overall ORs.

about 15–20% during the first week in hospital.[9] The findings in the present COMMIT trial of highly significant 15–20% relative reductions in reinfarction and ventricular fibrillation (although not in other types of cardiac arrest) with an average of about 2 weeks of metoprolol use early after MI strongly reinforce this evidence. Moreover, the observation that these reductions in reinfarction and ventricular fibrillation emerged gradually throughout the treatment period, with significant additional benefits after the first day or two, could be of particular relevance for the prevention of sudden cardiac death during the later period in hospital after acute MI when rapid defibrillation and other emergency care might not be so readily available.[29]

Cardiogenic shock

Previously there had been no definite evidence from randomised trials that early β-blocker therapy in acute MI produced an excess risk of cardiogenic shock (although such therapy was generally judged to be contraindicated in patients who had already developed shock). This lack of evidence was in part because information on shock was not collected systematically in many of the previous trials of early β-blocker therapy,[9] and in part because most of those trials mainly involved low-risk patients and only small numbers went rapidly into shock. By involving a much larger number of relatively unselected patients with acute MI, the COMMIT trial has been able to show that allocation to this intravenous then oral metoprolol regimen produced a highly significant 30% relative increase in the development of cardiogenic shock that is consistent across all the different types of patients studied (despite the care with which the intravenous regimen was titrated to avoid over-treatment). The present trial cannot assess directly whether this early excess of cardiogenic shock could have been largely avoided by starting with oral rather than with intravenous β-blocker treatment. Based on results of non-randomised comparisons of different atenolol regimens used in patients with acute MI, intravenous therapy has been reported to be associated with significantly higher rates of cardiogenic shock and congestive heart failure than oral therapy.[11] But this difference in risk in the observational study could be merely an artifact of selection bias (eg, difference in timing of initiation between different regimens).

The reported incidence of cardiogenic shock in the COMMIT population (about 4% in the placebo group) was somewhat lower than that found in routine clinical settings,[30,31] chiefly because patients who presented with shock, severe heart failure, or persistent hypotension were generally excluded before randomisation. However, the overall fatality rate (about 70%) in patients who subsequently did develop shock was similar to that reported in many other studies,[32,33] confirming that the observed excess represents a real hazard. Results of a small pharmacodynamic study had suggested that Chinese people may be less tolerant of β-blocker therapy than Europeans or Americans.[34] In the present study, titration of the intravenous regimen, according to the effects on blood pressure and heart rate, resulted in doses of metoprolol being given in this Chinese population that were similar to that in the previous MIAMI trial[7] done in a European population, and compliance with the oral metoprolol regimen in COMMIT was also similar to that in MIAMI (at least in similar types of low risk patients).

Net effects in low-risk patients

The overall balance of hazards and benefits of early β-blocker therapy in the COMMIT trial correlated strongly with the background risk of shock, and there were particularly large net hazards in patients at high risk of developing shock (such as those presenting in Killip class III or with low blood pressure). Although it was not possible to identify reliably any particular category of patients in which the beneficial effects of early β-blocker therapy clearly outweighed the adverse effects, there was a tendency towards net benefit in those at lower risk of developing shock. In a retrospectively-defined subgroup of COMMIT similar to the population studied in MIAMI (ie, Killip class I, systolic blood pressure higher than 105 mm Hg, and heart rate of more than 65 bpm[7]) the overall effects on death, reinfarction, and arrest were generally consistent with the results in previous trials, which mainly involved lower-risk patients (figure 4). Taking this finding and those of other trials together, in 52 000 similarly low-risk patients, immediate treatment with intravenous then oral β-blocker therapy was associated with a moderate, but highly significant, reduction in mortality (1265 [4·8%] vs 1436 [5·5%]; p=0·0006). Even so, allocation of such patients in COMMIT to receive metoprolol did not produce a significant reduction in the combined outcome of death, reinfarction, arrest, or shock during days 0–1 (518 [4·2%] metoprolol *vs* 535 [4·3%] placebo; p=0·76), and was associated with only a small, marginally significant, net benefit from day 2 onwards (516 [4·2%] vs 598 [4·8%], p=0·02).

Gaining benefits and avoiding hazard

Overall, no significant net effects were noted with early metoprolol therapy on mortality alone, or on the combined efficacy and safety outcome in the study as a whole. But, the risks of these different outcomes differed by period after randomisation and in different subcategories of patient, and hence so too did the balance of the effects of metoprolol. By contrast with the early excess risk of cardiogenic shock, the reductions in the risk of reinfarction and of ventricular fibrillation seemed to emerge more gradually. Consequently, the overall net effect of metoprolol therapy on the combined efficacy and safety outcome changed from being significantly adverse during days 0–1 to being significantly beneficial thereafter. Early after the onset of MI, higher-risk patients may be relatively poorly perfused and a rapid reduction in blood pressure with β-blocker therapy may further compromise their haemodynamic status.[35] The lack of any late excess of shock with continued metoprolol treatment seems likely to reflect the general improvement in the patients' condition, rather than the selective removal of susceptible patients by death or discontinuation early after hospital admission. As such, delaying the initiation of β-blocker therapy until after a patient's condition has stabilised after MI (thereby avoiding such treatment in persistently unstable patients) might avoid much of the excess risk of shock associated with β blockade while retaining much of the beneficial effect on reinfarction and ventricular fibrillation during the hospital stay. Starting with an intravenous regimen (or a short-acting oral agent) as a test dose while the patient is still under close observation might help further to reduce the potential hazard.

Conclusions

Early β-blocker therapy has been widely recommended as part of the emergency treatment of suspected acute MI, especially when there is tachycardia or hypertension.[2–4] Despite these recommendations, there has been ambivalence for many years about the appropriate use of intravenous β-blocker therapy, with wide variation in patterns of routine use within and between different countries (eg, 0·5% in the UK and 54% in Sweden).[11–14] This variation probably indicates uncertainty among clinicians about the appropriate extrapolation of previous trial evidence into clinical practice, as well as continuing concerns about the potential hazards of such therapy.[10,11,25] The present results confirm some of these concerns, but reduce others, and should help to guide more appropriate use of early β-blocker therapy in acute MI. Given the excess of cardiogenic shock, immediate β-blocker therapy cannot be recommended routinely. Instead, it may generally be more prudent to start β-blocker therapy only after a patient's haemodynamic condition has stabilised after MI, with the aim of preventing reinfarction and sudden cardiac death during the later period of the hospital stay.[9,28,29] If, as an additional consequence of the more widespread initiation of β-blocker therapy in hospital, more individuals are

discharged on long-term β-blocker therapy then the benefits of β-blocker therapy would be greater.

Contributors

All members of the writing committee contributed to the study design, its undertaking, data analysis, and interpretation of the study results, as well as to the writing of the manuscript.

Conflict of interest statement

The Clinical Trial Service Unit (writing committee members: Z M Chen, H C Pan, Y P Chen, R Peto, and R Collins) has a staff policy of not accepting honoraria or other payments from the pharmaceutical industry, except for the reimbursement of costs to participate in scientific meetings. Other members of the writing committee from Beijing Fuwai Hospital (L X Jiang, J X Xie, and L S Liu) have accepted honoraria from the pharmaceutical industry for lecturing in China.

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