β Blockade after myocardial infarction: systematic review and meta regression analysis

Nick Freemantle, John Cleland, Philip Young, James Mason, Jane Harrison

Medicines Evaluation Group, Centre for Health Economics, University of York, York YO10 5DD
Nick Freemantle, *senior research fellow*
James Mason, *senior research fellow*
Jane Harrison, *information officer*

Department of Cardiology, Castle Hill Hospital, University of Hull, Kingston upon Hull, U16 5JQ
John Cleland, *professor*

Department of Health Sciences and Clinical Evaluation, University of York
Philip Young, *lecturer in applied statistics*

Correspondence to: N Freemantle meg@york.ac.uk

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Abstract

Objectives To assess the effectiveness of β blockers in short term treatment for acute myocardial infarction and in longer term secondary prevention; to examine predictive factors that may influence outcome and therefore choice of drug; and to examine the clinical importance of the results in the light of current treatment.
Design Systematic review of randomised controlled trials.
Setting Randomised controlled trials.
Subjects Patients with acute or past myocardial infarction.
Intervention β Blockers compared with control.
Main outcome measures All cause mortality and non-fatal reinfarction.
Results Overall, 5477 of 54 234 patients (10.1%) randomised to β blockers or control died. We identified a 23% reduction in the odds of death in long term trials (95% confidence interval 15% to 31%), but only a 4% reduction in the odds of death in short term trials (– 8% to 15%). Meta regression in long term trials did not identify a significant reduction in effectiveness in drugs with cardioselectivity but did identify a near significant trend towards decreased benefit in drugs with intrinsic sympathomimetic activity. Most evidence is available for propranolol, timolol, and metoprolol. In long term trials, the number needed to treat for 2 years to avoid a death is 42, which compares favourably with other treatments for patients with acute or past myocardial infarction.
Conclusions β Blockers are effective in long term secondary prevention after myocardial infarction, but they are underused in such cases and lead to avoidable mortality and morbidity.

Introduction

β Blockade was once heralded as a major advance in the treatment of patients with myocardial infarction, but current evidence suggests that less than half of eligible patients receive it.[1–3] The effectiveness of β blockers was appraised by Yusuf et al in 1985,[4] but since then there have been nearly 3000 deaths among 23 000 patients randomised in new trials. Trials of β blockers now include a broader group of patients such as those at high risk or with accompanying heart failure, enabling the benefits identified by Yusuf et al[4] in a restricted group of trials to be extended to such patients.

Methods used in systematic reviews have also advanced. The development of regression techniques within meta analysis enables a more robust examination of the importance of factors that may mediate upon the effectiveness of specific drugs.[5] Two such factors, intrinsic sympathomimetic activity and cardioselectivity, were identified as potentially important,[4] and intrinsic sympathomimetic activity in particular seemed to be related to reduced therapeutic action. Given the changing use of drugs after myocardial infarction, the early promise of β blockade in these patients, and the continuing high rates of mortality associated with myocardial infarction, a new overview of these drugs is timely.

website *extra*

References for the trials appear on the BMJ's website

www.bmj.com

Methods

Objective

We reappraised the effectiveness of β blockers for secondary prevention after myocardial infarction. Our main outcome was all cause mortality and the secondary outcomes were non-fatal reinfarction and withdrawal from treatment. We examined the effectiveness of β blockers in the acute phase immediately after myocardial infarction; their role in longer term secondary prevention; the importance of early initiation after the onset of symptoms; the extent to which specific pharmacological features of different β blockers may affect their performance; the magnitude of benefits achieved by β blockers; and the clinical importance of β blockers.

Inclusion criteria

We included randomised trials without crossover, with treatment lasting more than one day, and with follow up that examined the clinical effectiveness of β blockers versus placebo or alternative treatment in patients who had had a myocardial infarction. Treatment may have begun at any stage before or after myocardial infarction and may have been commenced intravenously.

Search strategy

We conducted sensitive electronic searches of Medline (1966-97 through Ovid), Embase (1974-97 through Dialog), Biosis (1985-97 through Edina), Healthstar (1975-97 through Ovid), Sigle (1980-97 through Blaise-line), IHTA (1990-97 through ECRInet), conference papers index (1984-97 through Dialog), Derwent drug file (1992-97 through Dialog), dissertation abstracts (1992-97 through Dialog), Pascal (1992-97 through Dialog), international pharmaceutical abstracts (1992-97 through Dialog), and science citation index (1981-97 through BIDS).

We reviewed the reference list of each identified study. We also examined existing bibliographies and reviews for relevant studies.

Data abstraction and appraisal of study quality

From each study we abstracted data on the total number of patients randomised to active treatment or control, β blocker, route and dose of drug, duration of treatment, loss to follow up, level of blinding, concealment of allocation,[6] specific study inclusion and exclusion criteria, duration of follow up, deaths, reinfarc-

Table 1 Characteristics of short term trials comparing β blockers with control (see website for references)

Trial	Average follow up	Drug*	Blinding	Concealment of allocation	Loss to follow up (%)	Outcome or endpoint	Heart failure (%)	Mortality (No/total No)	
								β Blockers	Controls
Azancot 1982[w1]	1 month	Acebutolol*	No	Unclear	0	Mortality	0	0/14	0/12
Balcon 1966[w2]	28 days	Propranolol	Double	Unclear	0	Mortality	55	14/56	15/58
Barber 1976[w3]	4 weeks	Propranolol	No	Unclear	Unclear	Mortality, reinfarction	Unclear	10/52	12/47
Campbell 1984[w4]	In hospital	Timolol*	Unclear	Unclear	0	Mortality	Unclear	1/20	2/19
Clausen 1966[w5]	14 days	Propranolol	Unclear	Unclear	0	Mortality	Unclear	18/66	19/64
CPRG 1981[w6]	8 weeks	Oxprenolol	Double	Unclear	0	Mortality, reinfarction	0	9/177	5/136
Curtis 1991[w7]	3.4 days	Propranolol	Double	Unclear	0	Mortality	Unclear	0/18	0/12
Dotremont 1968[w8]	3-6 weeks	Propranolol	No	No	Unclear	Mortality	68.6	4/36	5/36
Evemy 1978[w9]	7 months	Practolol*	No	No	Unclear	Mortality	Unclear	9/46	6/48
Federman 1984[w10]	28 days	Timolol*	Unclear	Unclear	0	mortality	0	1/50	0/50
Fuccella 1968[w11]	21 days	Oxprenolol	Unclear	Unclear	14	Mortality	Unclear	15/106	9/114
Gupta 1982[w12]	Unclear	Propranolol	Unclear	Unclear	0	Mortality	Unclear	0/25	3/25
Gupta 1984[w13]	72 hours	Propranolol*	No	Unclear	Unclear	Mortality	Unclear	0/15	0/15
Heber 1987[w14]	1 year	Labetalol*	No	Unclear	Unclear	Mortality	Unclear	12/83	7/83
Hutton 1979[w15]	2 days	Propranolol	Unclear	Unclear	0	Mortality	Unclear	0/16	0/13
ICSG 1984[w16]	To discharge	Timolol	Double	Unclear	0	Mortality	57 being treated for heart failure	3/73	4/71
ISIS-1 Collaborative Group 1986[w17]	1 year	Atenolol*	No	NA	Unclear	Mortality	Unclear	1071/8037	1120/7990
Johansson 1980[w18]	6 months	Practolol* then atenolol	Single	No	Unclear	Mortality	Unclear	7/25	7/29
Kahler 1968[w19]	Up to 35 days	Propranolol	Double	Unclear	Unclear	Mortality, reinfarction	11	3/38	6/31
Ledwich 1968[w20]	7 days	Propranolol	Double	Unclear	Unclear	Mortality	Unclear	2/40	3/40
Lloyd 1988[w21]	72 hours	Sotalol*	No	Unclear	0	Mortality	Unclear	0/15	0/15
Lombardo 1979[w22]	20 days	Oxprenolol	Double	Unclear	Unclear	Mortality	0	8/133	11/127
Macleod 1980[w23]	1 week	Practolol*	Unclear	Unclear	0	Mortality	Unclear	1/26	0/26
McMurray 1991[w24]	7 days	Xamoterol	Double	Unclear	0	Mortality	31	0/25	0/26
MIAMI Trial Research Group 1985[w25]	15 days	Metoprolol*	Double	Yes	0.04	Mortality	23.5	123/2877	142/2901
Mueller 1980[w26]	To discharge	Propranolol*	Double	Unclear	Unclear	Mortality	Unclear	2/35	1/35
Multicentre 1966[w27]	28 days	Propranolol	Double	Unclear	1	Mortality	11	15/100	12/95
Nigam 1983[w28]	1 week	Propranolol*	Unclear	Unclear	0	Mortality	Unclear	0/20	0/20
Norris 1968[w80]	3 weeks	Propranolol	Double	Yes	0	Mortality	Unclear	31/226	24/228
Norris 1978[w29]	To discharge	Propranolol*	No	No	Unclear	Mortality	Unclear	0/20	0/23
Norris 1984[w30]	In hospital	Propranolol*	No	NA	0	Mortality	Unclear	15/364	14/371
Owensby 1984[w31]	3 days	Pindolol*	No	NA	Unclear	Mortality	Unclear	1/50	1/50
Peter 1978[w32]	To discharge	Propranolol*	No	Unclear	0	Mortality	0	1/47	2/48
Pitt 1976[w33]	14 days	Propranolol	Double	Unclear	0	Mortality	Unclear	0/9	0/8
Ranganathan 1988[w34]	28 days	Timolol*	Double intravenously then by open label orally	Unclear	2	Mortality	Unclear	1/45	3/49
Roberts 1984[w35]	36 months	Propranolol*	Single	Unclear	0.2	Mortality	4.9	24/134	20/135
Singh 1985[w36]	60 hours	Propranolol*	No	Unclear	0	Mortality	Unclear	0/8	0/7
Sloman 1967[w37]	To discharge	Propranolol*	No	Unclear	Unclear	Mortality	Unclear	3/26	4/23
Snow 1980[w38]	Short term	Practolol	Unclear	Unclear	0	Mortality	Unclear	19/76	15/67
Thompson 1979[w39]	1 year	Practolol	Double	Unclear	Unclear	Mortality	Unclear	5/72	6/71
TIMI IIB Study Group 1989[w40]	5 days	Metoprolol* (15 mg)	No	Unclear	3.5	Mortality, reinfarction	1.1	17/696	17/694
Tonkin 1981[w41]	1 year	Timolol	Double	Unclear	Unclear	Mortality, reinfarction	Unclear	1/42	1/46
UKCSG 1983[w42]	To discharge	Timolol	Double	Unclear	Unclear	Mortality	Unclear	4/56	5/55
Van de Werf 1993[w43]	10-14 days	Atenolol	Double	Unclear	0	Mortality, reinfarction	Unclear	1/100	4/94
Von Essen 1982[w44]	14 days	Metoprolol*	Double	Unclear	0	Mortality	Unclear	1/25	1/26
Waagstein 1975[w45]	1 week	Practolol,* H87/07, or metoprolol	Double	Unclear	0	Mortality	Unclear	0/38	0/45
Wilcox 1980b[w46]	6 weeks	Oxprenolol	Double	Yes	0	Mortality	28 withdrawn owing to severe heart failure	14/157	10/158
Yang 1987[w47]	14 days	Betaxolol	Double	Unclear	0	Mortality	9.4	0/16	0/15
Yusuf 1980[w48]	10 days for infarction, 1-4 years for mortality	Atenolol*	No	Unclear	Unclear	Mortality, morbidity	6.5	36/244	44/233

CPRG=Coronary Prevention Research Group; ICSG=International Collaborative Study Group; ISIS-1=first international study of infarct survival; MIAMI=metoprolol in acute myocardial infarction; TIMI IIB=thrombolysis in myocardial infarction phase II trial; UKCSG=UK Collaborative Study Group. *Initial dose intravenously.

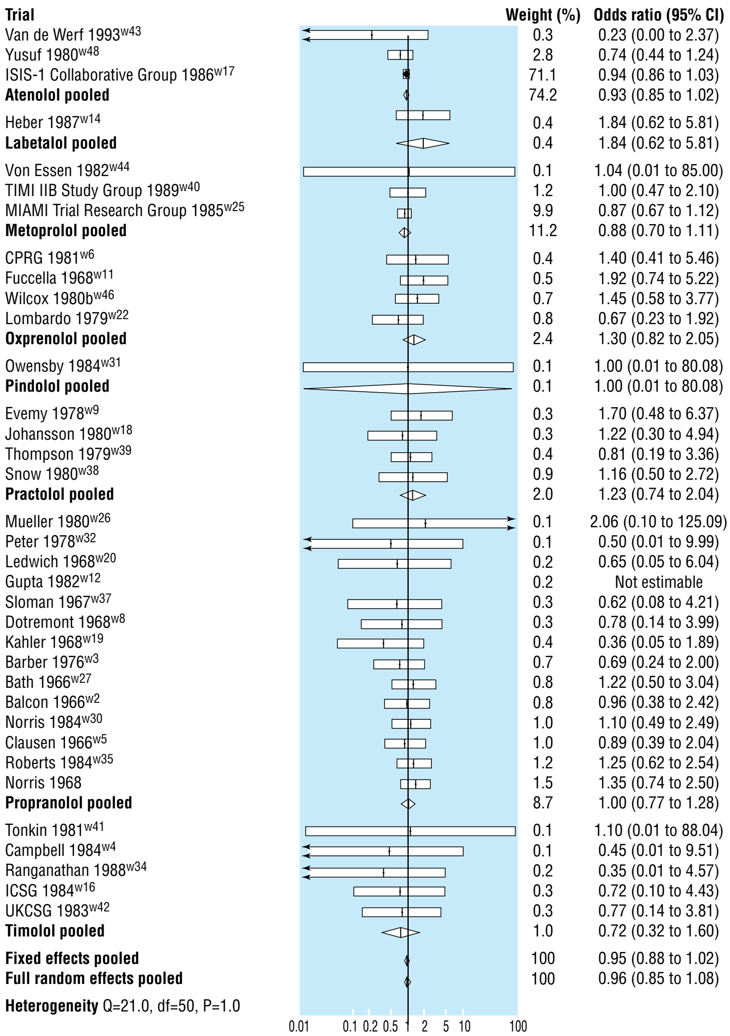


Fig 1 Odds of death and pooled odds ratios in short term trials (arrows indicate 95% confidence intervals exceeding range of plot). ISIS-1=first international study of infarct survival; TIMI IIB=thrombolysis in myocardial infarction phase II trial; MIAMI=metoprolol in acute myocardial infarction; CPRG=Coronary Prevention Research Group; ICSG=International Collaborative Study Group; UKCSG=UK Collaborative Study Group

tions, and withdrawals. Data were checked by a second researcher.

Statistical analysis

We estimated pooled odds ratios for short and long term treatment trials separately using the fixed effects approach of Mantel Haenszel.[7 8] As we anticipated systematic differences between the results of studies (heterogeneity), we also routinely estimated random effects pooled odds ratios. Standard random effects methods for meta-analysis (pooling the results of studies)[9 10] may provide unduly precise estimates of effect, as they assume that the observed distribution of effects is the true treatment distribution—an assumption that may not be valid in sparse data.[5 11 12] Therefore, we used the full random effects approach on the basis of the numerical integration techniques using Markov chain Monte Carlo simulation, with appropriate uninformative priors and the "Bugs" software described by Smith et al.[5] This provides a more robust estimate of the precision of random effects estimates and can account for trial groups that experience no events without resorting to crude fixes such as adding a value to each cell to estimate an individual odds ratio. A further advantage of this approach is that the effects of predictive factors may be examined. Our main treatment related covariates were cardioselectivity and intrinsic sympathomimetic activity, which were examined in the long term trials using a nested random effects logistic regression model (see appendix).

We also made a separate examination of the effects of initial intravenous treatment in long term trials, and the effect of additional treatment options through the proxy variable of publication date before or after the median year (1982). We assessed convergence using the methods described by Geweke[13] and visual inspection of convergence plots.

We calculated risk differences using standard random effects methods,[11] and because comparison of risk differences between trials may be affected by different lengths of follow up, we also estimated a pooled incidence risk difference using the approach described by Ioannidis et al.[14] This is less robust than the pooled odds ratio but provides a practically interpretable estimate of absolute treatment effect derived directly from the trials.[15] For the long term trials, we also calculated pooled estimates of effect for each β blocker using the fixed effects model.[7 8]

Results

We identified 82 randomised trials that examined the effects of β blockers compared with control and that had data on all cause mortality. Overall, 5477 of 54 234 patients (10.1%) randomised died. Fifty one trials examined acute treatment with β blockers—up to 6 weeks after onset of pain (table 1, and 31 trials examined long term treatment with β blockers—6 to 48 months (table 2).

Short term trials

Overall, 3062 of 29 260 patients (10.5%) randomised in short term trials died. Although 51 trials were identified that examined the effects of short term treatment, only 45 of these had observed deaths in either the intervention or control groups. The major challenge to the quality of this group of trials was that small numbers of patients randomised to treatment or control led to many trials with either no, or only a small number of, deaths.

The pooled random effects odds ratio for the short term trials was 0.96 (95% confidence interval 0.85 to 1.08); that is, a small and non-significant reduction in the odds of death (fig 1). Even if this result is correct it would represent a reduction of only 0.4 deaths in 100 patients, which does not achieve conventional levels of significance (−0.2 to 1) as 250 patients would require treatment to avoid one death (100 to ∞). Analysis of predicted benefit by drug identified no individual drug that differed significantly in effect from the pooled result.

Although most trials were undertaken before the second international study of infarct survival in 1988[16] firmly established the importance of thrombolysis, a large trial of thrombolysis in myocardial infarction in 1989[17] randomised patients who had received recombinant tissue plasminogen activator within 4 hours of

Table 2 Characteristics of long term trials comparing β blockers with control (see website for references)

Trial	Average follow up	Drug*	Blinding	Concealment of allocation	Loss to follow up (%)	Outcome or endpoint	Heart failure (%)	Mortality (No/total No)		No of reinfarctions		No of withdrawals	
								β blockers	Controls	β blockers	Controls	β blockers	Controls
Ahlmark 1974[w49]	2 years	Alprenolol	Unclear	Unclear	Unclear	Mortality, reinfarction	Unclear	5/69	11/93	4	15	4	6
Andersen 1979[w50]	About 1 year	Alprenolol	Double	Unclear	0	Mortality	Unclear	61/238	64/242	—	—	59	49
Boissel 1990[w51]	318 days	Acebutolol	Double	Yes	0	Mortality	49.5	17/298	34/309	—	—	102	109
Aronow 1997[w52]	1 year	Propranolol	Unclear	Unclear	Unclear	Mortality, reinfarction	100	44/79	60/79	3	5	—	—
Australian and Swedish study 1983[w53]	2 years	Pindolol	Double	Unclear	Unclear	Mortality, reinfarction	61 left ventricular dysfunction	45/263	47/266	12	13	76	50
Baber 1980[w54]	9 months	Propranolol	Double	Unclear	Unclear	Mortality, reinfarction	Unclear	28/355	27/365	17	27	82	88
Barber 1967[w55]	2 years	Practolol	Unclear	Unclear	Unclear	Mortality, reinfarction	26	33/207	38/213	—	—	—	—
Basu 1997[w56]	6 months	Carvedilol	Double	Unclear	0	Mortality, reinfarction	45	2/75	3/71	4	8	—	—
BHAT 1982[w57]	25 months	Propranolol	Double	Yes	0.3	Mortality	9.2	138/1916	188/1921	103	121	243	179
Darasz 1995[w58]	6 months	Xamoterol	Double	Unclear	19	Mortality, reinfarction		3/23	1/24	—	—	3	6
EIS 1984[w59]	1 year	Oxprenolol	Double	Unclear	Unclear	Mortality, Reinfarction	7.7	57/853	45/883	36	38	275	275
Hansteen 1982[w60]	1 year	Propranolol	Double	Unclear	0	Mortality, reinfarction	5.9 (taking digitalis)	25/278	37/282	16	21	70	72
Hjalmarson 1981[w61]	2 years	Metoprolol*	Double (3 months) then open treatment (to 2 years)	Unclear	1.6	Mortality at 2 years; reinfarction at 3 months	10	40/698	62/697	35	54	131	131
Julian 1982[w62]	12 months	Sotalol	Double	Yes	0	Mortality, reinfarction	0	64/873	52/583	37	38	218	121
Kaul 1988[w63]	6 months	Propranolol (iv)	Double	Unclear	0	Mortality, reinfarction	Unclear	3/25	3/25	0	4	0	0
LIT Research Group 1987[w64]	18 months	Metoprolol	Double	Unclear	0.2	Mortality	2.1	86/1195	93/1200	—	—	381	355
Manger Cats 1983[w65]	1 year	Metoprolol	Double	Unclear	0	Mortality	Unclear	9/273	16/280	—	—	—	—
Mazur 1984[w66]	1.5 years	Propranolol	No	Unclear	Unclear	Mortality, reinfarction	Unclear	5/101	11/103	5	7	—	—
Multicentre international 1975[w67]	Up to 24 months	Practolol	Double	Unclear	3.4	Mortality, reinfarction	0	102/1533	127/1520	69	89	389	382
Norwegian Multicentre Study Group 1981[w68]	17 months	Timolol	Double	Unclear	Unclear	Mortality	33	98/945	152/939	88	141	275	219
Rehnqvist 1980[w69]	1 year	Metroprolol	Unclear	Unclear	0	Mortality	Unclear	4/59	6/52	—	—	12	5
Rehnqvist 1983[w70]	36 months	Metoprolol	Double	Unclear	0	Mortality, reinfarction	24 (taking digitalis)	25/154	31/147	18	31	38	35
Reynolds 1972[w71]	1 year	Alprenolol	Double	Yes	Unclear	Mortality, reinfarction	Unclear	3/38	3/39	3	2	4	3
Roqué 1987[w72]	24 months	Timolol*	Double	Unclear	Unclear	Mortality	Unclear	7/102	12/98	—	—	—	—
Salathia 1985[w73]	1 year	Metoprolol*	Double	Unclear	0.5	Mortality,	10	49/416	52/348	—	—	95	66
Schwartz 1992 (high risk and low risk)[w74]	22 months	Oxprenolol	High risk† and low risk‡ groups	Unclear	0	Mortality, reinfarction	2 in high risk group; unclear for low risk group	2/48 15/437	12/56 27/432	0	2	11	9
SSSD 1993[w75]	3 years	Metoprolol	No	Unclear	1.9	Mortality, reinfarction	100	17/130	9/123	5	6	—	—
Taylor 1982[w76]	48 months	Oxprenolol	Double	Done	Unclear	Mortality, reinfarction	0	60/632	48/471	67	58	185	141
Wilcox 1980a[w77]	1 year	Propranolol* or atenolol	Double	Done	0	Death	Unclear	19/127 17/132	19/129	—	—	44 51	40 40
Wilhelmsson 1974[w78]	2 years	Alprenolol	Double	Unclear	7	Mortality	Unclear	7/114	14/116	16	18	8	8
Yusuf 1979[w79]	12 months	Atenolol	Double	Unclear	23	Death; electrocardiographic signs	Unclear	1/11	1/11	—	—	2	1

BHAT=β-blocker heart attack trial; LIT=lopressor intervention. *Initial dose intravenously. †Single blind. ‡Double blind.

Trial	Weight (%)	Odds ratio (95% CI)
Boissel 1990[w51]	2.9	0.49 (0.25 to 0.93)
Acebutolol pooled	2.9	0.49 (0.25 to 0.93)
Reynolds 1972[w72]	0.3	1.03 (0.13 to 8.21)
Ahlmark 1974[w49]	0.8	0.58 (0.15 to 1.94)
Wilhelmsson 1974[w79]	1.2	0.48 (0.16 to 1.33)
Andersen 1979[w50]	4.3	0.96 (0.62 to 1.47)
Alprenolol pooled	6.6	0.83 (0.59 to 1.17)
Wilcox 1980a[w78]	0.1	1.02 (0.48 to 2.16)
Yusuf 1979[w80]	1.5	1.00 (0.01 to 86.25)
Atenolol pooled	1.6	1.02 (0.52 to 1.99)
Basu 1997[w56]	0.3	0.62 (0.05 to 5.61)
Carvedilol pooled	0.3	0.62 (0.05 to 5.61)
Rehnqvist 1980[w70]	0.7	0.56 (0.11 to 2.53)
López 1993[w75]	1.4	1.91 (0.76 to 5.05)
Manger Cats 1983[w65]	2.4	0.55 (0.21 to 1.36)
Rehnqvist 1984[w71]	4.6	0.73 (0.39 to 1.35)
Salathia 1985[w73]	5.4	0.76 (0.49 to 1.18)
LIT Research Group 1987[w64]	7.9	0.92 (0.67 to 1.27)
Hjalmarson 1981[w61]	0.5	0.62 (0.40 to 0.96)
Metoprolol pooled	23.1	0.80 (0.66 to 0.96)
European infarction study 1984[w58]	1.0	1.33 (0.87 to 2.04)
Schwartz 1992[w74] (high risk)	2.4	0.16 (0.02 to 0.79)
Schwartz 1992[w74] (low risk)	3.8	0.53 (0.26 to 1.06)
Taylor 1982[w76]	4.6	0.92 (0.61 to 1.41)
Oxprenolol pooled	11.8	0.91 (0.71 to 1.17)
Australian and Swedish study 1983[w53]	3.6	0.96 (0.60 to 1.55)
Pindolol pooled	3.6	0.96 (0.60 to 1.55)
Barber 1967[w55]	2.9	0.87 (0.51 to 1.50)
Multicentre international study 1975[w67]	11.0	0.78 (0.59 to 1.03)
Practolol pooled	13.9	0.80 (0.63 to 1.02)
Kaul 1988[w63]	2.4	1.00 (0.12 to 8.31)
Mazur 1984[w66]	0.2	0.44 (0.11 to 1.43)
Wilcox 1980a[w78]	1.5	0.86 (0.40 to 1.84)
Baber 1980[w54]	2.3	1.07 (0.59 to 1.93)
Aronow 1997[w52]	3.1	0.40 (0.19 to 0.83)
Hansteen 1982[w60]	16.0	0.65 (0.37 to 1.15)
BHAT Trial Research Group 1982[w57]	1.0	0.72 (0.56 to 0.91)
Propranolol pooled	26.6	0.71 (0.59 to 0.85)
Julian 1982[w62]	5.3	0.81 (0.54 to 1.21)
Sotalol pooled	5.3	0.81 (0.54 to 1.21)
Roqué 1987[w77]	1.0	0.53 (0.17 to 1.54)
Norwegian Multicentre Study Group 1981[w68]	12.6	0.60 (0.45 to 0.79)
Timolol pooled	13.6	0.59 (0.46 to 0.77)
Darasz 1995[w69]	0.1	3.45 (0.25 to 188.83)
Xamoterol pooled	0.1	3.45 (0.25 to 188.83)
Fixed effects pooled	100	0.77 (0.70 to 0.84)
Full random effects pooled	100	0.77 (0.69 to 0.85)

Heterogeneity Q=39.7, df=32, P=0.16

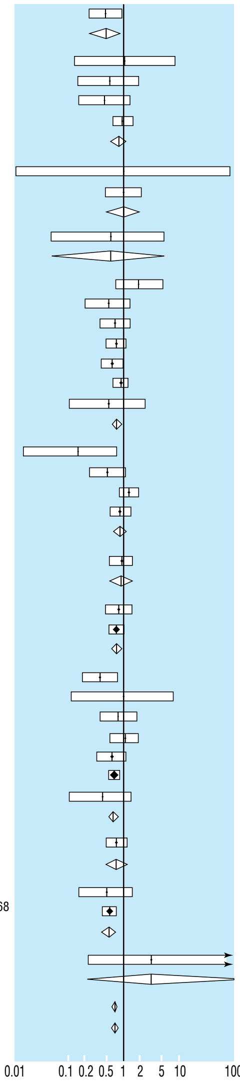


Fig 2 Odds of death and pooled odds ratios in long term trials. LIT=lopressor intervention; BHAT=β-blocker heart attack trial

the onset of pain to early metoprolol or control. During 5 days of follow up, there was no difference in mortality between the two groups. Two subsequent myocardial infarctions were, however, avoided for every 100 patients treated (0.2 to 4).

Long term trials

Overall effects

Overall, 2415 of 24 974 patients (9.7%) randomised in the 31 long term trials died. In general, the quality of studies was reasonably high, with adequate follow up achieved in many trials (table 2), though the proxy quality variable, concealment of allocation, was seldom adequately reported.

Overall, the pooled odds ratio from the full random effects model was 0.77 (0.69 to 0.85). Results from the standard fixed effects model were similar (fig 2).

Because of potential confounding due to the differences in length of study follow up, we used the random effects approach for incidence of risk difference to estimate the normalised annual reduction in mortality across the trials. This approach suggests an annual reduction of 1.2 deaths in 100 patients treated with β blockers after myocardial infarction (0.6 to 1.7); that is, about 84 patients will require treatment for 1 year to avoid one death. A similar approach was used to estimate the effects of treatment on reinfarction, although only 21 of the 34 comparisons provided data on reinfarction, resulting in wider confidence intervals and the potential for reporting bias. This analysis suggests an annual reduction in reinfarction of 0.9 events in every 100 (0.3 to 1.6); that is, about 107 patients would require treatment for 1 year to avoid one non-fatal reinfarction.

Predictors of benefit

Initial intravenous dose—We investigated the extent to which initiation of treatment with an intravenous dose of β blockers predicted mortality in the long term trials. Applying initial intravenous dose as a covariate term in the analysis suggested no additional benefit among patients treated in this manner (odds ratio 0.87, 0.61 to 1.22). Equally, this analysis indicates that there is no reason to delay treatment with a β blocker and that early initiation will lead to a greater period when benefits may be accrued from treatment.

Presence of cardioselectivity or intrinsic sympathomimetic activity—We anticipated that the presence of cardioselectivity and intrinsic sympathomimetic activity would be important predictors of benefit in the trials, a hypothesis examined by Yusuf et al.[4]

Classification of β blockers into those with or without important cardioselective activity or intrinsic sympathomimetic effect is not clear cut, and there is some debate in the literature on the attributes of acebutolol in particular.[18–20] Table 3 describes the attributes of β blockers used in the trials.

The odds ratio for the predictive effect of cardioselectivity on mortality was 1.10 (0.89 to 1.39), showing a non-significant trend towards reduced benefits. The odds ratio for the predictive effect of the presence of intrinsic sympathomimetic activity was 1.19 (0.96 to 1.47), which approaches statistical significance. The results were not sensitive to the classification of acebutolol.

Reduction of benefits over time—We investigated whether benefits were reduced in the trials with additional therapeutic options for treatment intro-

Table 3 Classification of attributes of different β blocker drugs

β Blocker	Cardioselectivity	Intrinsic sympathomimetic activity
Acebutolol	−	−
Alprenolol	−	+
Atenolol	+	−
Betaxolol	+	−
Carvedilol	−	−
Labetalol	−	−
Metoprolol	+	−
Oxprenolol	−	+
Pindolol	−	+
Practolol	+	+
Propranolol	−	−
Sotalol	−	−
Timolol	−	−
Xamoterol	+	+

+=Significant activity; −=no significant activity.

duced, in particular the increasing use of thrombolytic treatment, and aspirin. There is no evidence that treatment in trials after 1982 (the median trial) led to differences in benefit (odds ratio 1.04, 0.82 to 1.28).

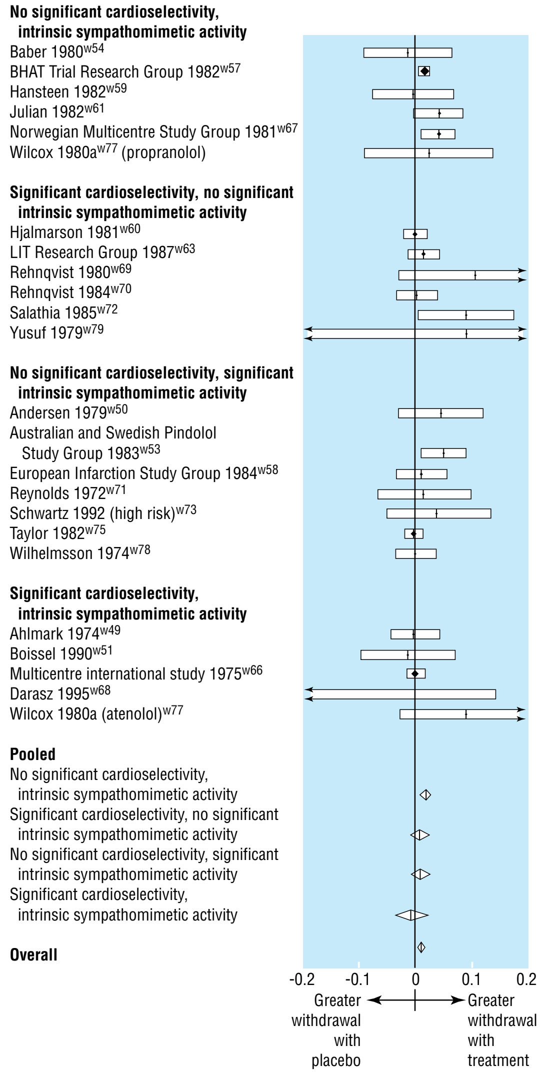
Choice of drug—Individually, only four drugs achieved a statistically significant reduction in the odds of death: propranolol (0.71, 0.59 to 0.85); timolol (0.59, 0.46 to 0.77); metoprolol (0.80, 0.66 to 0.96); and acebutolol (0.49, 0.25 to 0.93). The effectiveness of acebutolol is supported by a single moderately sized study, which is open to considerable measurement error. However, trials including propranolol, timolol, and metoprolol include 63% of the available evidence on the effects of long term β blockade in patients who have had a myocardial infarction.

Withdrawal from treatment

Different definitions and reporting made comparison of withdrawal of treatment withdrawal between trials problematic. Similar withdrawal rates between active treatment and placebo groups concealed two opposing effects: more patients are withdrawn from treatment groups because of suspected adverse cardiovascular reactions (most commonly brachycardia and hypotension), whereas in the placebo group withdrawal is more common because of the need for β blockade for hypertension and angina. Trials reports of dizziness, depression, cold extremities, and fatigue were only marginally more common in the treatment than control groups.

Withdrawal in trials from both treatment and control groups varied from 10% to 30%. No adequate studies have been retrieved to compare directly the comparative tolerability of β blockers with different cardioselectivity or intrinsic sympathomimetic activity.

Overall, 5151 of 21 954 patients (23.5%) withdrew from treatment (table 2). Overall, withdrawal was slightly more common in patients taking β blockers—the difference in the annualised rate of withdrawal compared with placebo being 1.16 in 100 patients treated (0.56 to 1.76, random effects; fig 3). No clinically important differences in withdrawal were observed between β blockers of differing cardioselectivity and intrinsic sympathomimeticity.



Pooled incident risk difference=0.0116 (95% CI 0.0056 to 0.0176)

Q (combinability for risk difference)=22.7, df=21, P=0.478

Fig 3 Incidence (yearly) of withdrawal from trials

Table 4 Comparison of effect on mortality of different drugs

Drug	Number needed to treat*
β Blockers	42
Angiotensin converting enzyme inhibitors	No long term trials in unselected patients
Antiplatelet agent[22]	153
Statin[29]	94
Calcium channel blockers (diltiazem)[30]	∞
Thrombolysis and aspirin for 4 weeks[16]	24
Warfarin[31 32]	63

*Number needed to avoid death in 2 years of treatment in unselected patients after myocardial infarction.

Discussion

Considerable evidence supports the routine long term use of β blockers in patients who have had a myocardial infarction, with substantial benefits in terms of reduced mortality and morbidity. Short term β blockade immediately after acute myocardial infarction seems unlikely to be of major benefit unless treatment is continued long term. This finding contradicts recent suggestions that β blockers should be more commonly used intravenously in acute myocardial infarction.[21] In fact, evidence strongly indicates that unless β blockers are continued long term, the benefits suggested by Owen[21] will not be observed.

The benefits of β blockers on all cause mortality are impressive when compared with other frequently used long term treatments for the same patient group. Table 4 shows the effects of different drugs on the number of patients that would need to be treated for 2 years to avoid one death—for example, after a myocardial infarction 42 patients would need to be treated with β blockers whereas 292 patients would need to be treated with antiplatelets.[22] The number and length of long term trials showing a consistent benefit for β blockers in unselected patients after myocardial infarction suggest lasting benefits in this comparatively high risk group, and suggest that β blockers should be continued indefinitely.

Have benefits from β blockade declined with availability of new treatments?

Our finding that β blockers benefit a broader group of patients after myocardial infarction supports the findings of the β blocker pooling project.[23] Our finding also agrees with those of the cooperative cardiovascular project, which examined the medical records of 201 752 patients who had had a myocardial infarction.[24] In that study, mortality was lower in every subgroup of patients treated with β blockade than in untreated patients. The findings of the cooperative cardiovascular project agree with our meta regression analysis, which found no evidence of a reduction in benefits from β blockade in more recent randomised trials. Indeed, rather than being overtaken by newer treatments, β blockers have a comparatively large effect in reducing mortality (table 4).

Which β blocker?

Cardioselectivity was associated with a non-significant trend towards reduced benefit. The presence of an intrinsic sympathomimetic effect predicted a near significant reduction in benefits and thus drugs with this characteristic should be avoided. We found evidence to support the long term use of propranolol and timolol, the only two drugs indicated for prophylaxis after myocardial infarction in the *British National Formulary*. The use of either drug led to a substantial reduction in the odds of death, with narrow confidence intervals (fig 2). In contrast, atenolol, which is commonly prescribed in secondary prevention, has been inadequately evaluated in this setting. Although similar efficacy may be achieved—we found no evidence that all β blockers are not equal—it cannot be presumed that the benefits from propranolol, timolol, and metoprolol will be achieved with other drugs.

Have benefits from intravenous β blockers declined over time?

It may be hypothesised that intervention with thrombolytic drugs and antiplatelets reduces the potential for patients to benefit from intravenous β blockade. The first international study of infarct survival[25] was completed before the results of the second international study[16] became available, and before the use of thrombolytic and antiplatelet treatment was established. In contrast, the comparison of early versus delayed β blockade in a large trial of thrombolysis in myocardial infarction was undertaken in patients who all received thrombolytic and antiplatelet treatment.[17] Although the much larger first international study of infarct survival trial[25] achieved a slightly larger reduction in the odds of death with β blockers, measurement error could not be excluded as an explanation for this difference, as indicated by the test for heterogeneity between the trials ($Q=0.025$, $df=1$, $P=0.87$). The thrombolysis in myocardial infarction trial did suggest that early use of intravenous β blockers could reduce the early risk of serious arrhythmias.

Are β blockers underused?

Concern has been voiced that β blockers are used in less than half of eligible patients after myocardial infarction,[1–3] despite substantial benefits and generally low treatment costs. Concern that side effects affect the usefulness of β blockers must be tempered by the low yearly withdrawal from β blockers in the long term trials we reviewed. The clinical implications of our results are clear. New is not necessarily better, especially if the aim is to reduce mortality in patients after myocardial infarction. Furthermore, the underuse of β blockers in this group leads to a rate of avoidable death that should not be considered acceptable among those keen to practice evidence based medicine.

Renewed interest in β blockers, particularly in patients with heart failure,[26–28] may lead to substantial benefits for a broad range of patients.

Key messages

- The first randomised trials of β blockade in secondary prevention after myocardial infarction were published in the 1960s
- β blockers were once heralded as a major advance, but their use for secondary prevention has declined in recent years
- Firm evidence shows that long term β blockade remains an effective and well tolerated treatment that reduces mortality and morbidity in unselected patients after myocardial infarction
- The benefits from β blockade compare favourably with other drug treatments for this patient group
- Most evidence is for propranolol, timolol, and metoprolol, whereas atenolol, which is commonly used, is inadequately evaluated for long term use

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Appendix

Statistical model for random effects regression analysis

$$\log\left(\frac{pt}{1-pt}\right)=\alpha+\delta+\beta I+\gamma S$$

$$\log\left(\frac{pc}{1-pc}\right)=\alpha$$

Where pt is the probability of an event in the intervention group, pc is the probability of an event in the control group, *I* is the presence or absence of significant intrinsic sympathomimetic activity, and *S* is the presence or absence of significant cardioselectivity. Similarly, α is a constant, δ describes the overall treatment effect, β describes the effect of intrinsic sympathomimetic activity, and γ describes the effect of cardioselectivity.

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Risk factors for human hantavirus infection: Franco-Belgian collaborative case-control study during 1995-6 epidemic

N S Crowcroft, A Infuso, D Ilef, B Le Guenno, J-C Desenclos, F Van Loock, J Clement

Puumala hantavirus is the most common human hantavirus infection in Europe.[1 2] It is transmitted to humans by inhalation or contamination of skin breaches by urine or faeces of infected bank voles. Infection ranges from subclinical to a severe influenza-like illness progressing to acute renal failure.[3] We carried out a case-control study in an endemic area in France and Belgium to estimate knowledge of hantavirus and identify possible risk factors for infection.

Subjects, methods, and results

National reference laboratories in each country identified cases for the study. A case was defined as someone with laboratory confirmed IgM positive *Puumala hantavirus* infection between 1 April 1996 and 31 July 1996 in the French departments Nord, Ardennes, and Aisne and Belgian provinces of Hainaut, Namur, and Luxembourg. Controls were matched by sex, community (village), and age group. They were randomly selected from the telephone book. Interviews were carried out by telephone using a standardised questionnaire covering knowledge of hantavirus, distance of the home to a forest, refuse disposal, rodent infestation and control, gardening activities, use of wood for heating or cooking, activities in forests, and entry into rodent infested buildings.

In all, 69/88 (78%) eligible cases were included in the study and 125 controls were recruited. Most cases were in men (51) and those aged 15-65 years (64). Two cases and one control were forestry workers—no others were in occupations thought to be at risk. Forty seven per cent (91/194) of those interviewed had heard of hantavirus infection before becoming ill or being interviewed. Friends were the commonest source of information (44/91, 48%); 63/75 (84%) had heard of the disease in the past 3 years.

The table shows the results of logistic regression. Cases and controls often went walking in forests (odds ratio 0.5, 95% confidence interval 0.1 to 2.7; P = 0.64). Cases were more likely to have entered a building where there might be rodents (1.9, 1.0 to 3.6; P = 0.05) and were more likely to have cleaned (4.2, 1.1 to 15.7;

Epidemiology Department, Scientific Institute of Public Health—Louis Pasteur, Brussels, Belgium
N S Crowcroft, *fellow, European programme for intervention epidemiology training*
J-C Desenclos, *head of infectious diseases unit*

Réseau National de Santé Publique, Saint-Maurice, France
A Infuso, *fellow, European programme for intervention epidemiology training*
F Van Loock, *epidemiologist*

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