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Major β blocker mortality trials in chronic heart failure: a critical review

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This review examines, in detail, the three large, published, analyses of the effect of β adrenoceptor antagonist (β blocker) treatment on mortality in patients with chronic heart failure (CHF) caused by left ventricular systolic dysfunction. Two of these reports also describe the effect of treatment on morbidity and this is also reviewed. Lastly, β blocker tolerability, adverse effects, and dosage achieved are also examined. The three mortality reports are compared and contrasted in all these respects and also from the point of view of trial design, inclusion/exclusion criteria, and patients recruited. Conclusions regarding the use of β blockers in patients with CHF, in routine clinical practice, are then drawn from this overview.

Comparison of the three mortality reports is somewhat complicated by the fact that one of the reports concerns a pooled analysis of four small studies, individually set up to examine the effect of treatment on non-fatal (mainly symptomatic/exercise tolerance) end points (this was the United States carvedilol programme (USCP)).[1–5] The other two studies—the second cardiac insufficiency bisoprolol study (CIBIS II) and the metoprolol CR/XL randomised intervention trial in heart failure (MERIT-HF)—were single, prospective, mortality trials.[6–9] The USCP also differed from the other two trials in further important ways, including use of a prerandomisation "open label" run-in period and in having a much shorter follow up. All of these features make comparison of the USCP and the other two trials difficult. By contrast, CIBIS II and MERIT-HF are really quite similar in design and outcomes.

Table 1 Component trials of USCP

Trial	*Number of patients*	*Carvedilol: placebo*	*NYHA II/III (%)*	*Primary end point*
Mild CHF	366	2:1	85/15	Progression of CHF
MOCHA	345	3:1	46/52	Exercise tolerance (DRS)
PRECISE	278	1:1	40/57	Exercise tolerance
Severe CHF	105	2:1	0.5/86	QoL

DRS, dose response study; QoL, quality of life

Table 2 End points of component trials of USCP

Trial	*Primary end point*	*Other end points*
Mild	Progression of CHF*	LVEF*, NYHA class*, HF score*, global assessment*, QoL, 9 min SPT, heart size on CXR (death*)
Moderate (MOCHA)	6 min walk 9 min SPT	LVEF*, CHF hospitalisation*, (QoL, global assessment, death*)
Moderate (PRECISE)	6 min walk* 9 min SPT	Global assessment*, NYHA class*, LVEF*, QoL, CV hospitalisation*
Severe	QoL	Death, CV hospitalisation, global assessment*, NYHA class, LVEF*, 6 min walk

*Significant, between group, difference; CV, cardiovascular; CXR, chest radiography; HF, heart failure score; QoL, quality of life; SPT, self powered treadmill; for rest of key see text.

US carvedilol programme

AIM OF STUDY

Details of the four trials comprising the USCP are given in tables 1–9 and fig 1.

The individual component trials had varying primary and secondary end points (tables 1 and 2, fig 1). A prospective pooling of deaths in all four trials was, however, planned because of concerns that new drugs for CHF can increase mortality (table 3). The USCP, therefore, set out to recruit a sufficient number of patients to rule out (with 95% confidence) a 33% increase in the risk of death with carvedilol, compared to placebo (assuming an annual mortality rate of 12%). Because it was recognised that carvedilol might also reduce mortality, all statistical analyses were two sided. No formal stopping rules had been drawn up for the programme.

ENTRY CRITERIA

The USCP trials differed in two fundamental ways from CIBIS II and MERIT-HF (table 3). In the USCP trials patients had to undergo an "open label" run-in phase where they received unblinded carvedilol treatment for two weeks. Only patients tolerating 6.25 mg of carvedilol twice daily were eligible for randomisation. Clearly, therefore, this approach excludes patients unable to tolerate β blocker treatment. This approach to patient selection is controversial and it is difficult to know how to analyse events occurring during the run-in phase (see below). This approach also makes it difficult to assess adverse event rates and the proportion of patients achieving the target dose of test drug (see below). CIBIS II and MERIT-HF did not have a run-in phase.

Trial acronyms

BEST: β Blocker Evaluation Survival Trial
CIBIS: Cardiac Insufficiency Bisoprolol Study
COMET: Carvedilol or Metoprolol European Trial
COPERNICUS: Carvedilol Prospective Randomised Cumulative Survival Trial
DIG: Digitalis Investigation Group
ELITE: Evaluation of Losartan In The Elderly
MERIT-HF: Metoprolol CR/XL Randomised Intervention Trial in Heart Failure
MOCHA: Multicentre Oral Carvedilol Heart failure Assessment
PRAISE: Prospective Randomised Amlodipine Survival Evaluation
PRECISE: Prospective Randomised Evaluation of Carvedilol on Symptoms and Exercise
PRIME: Prospective Randomised study of Ibopamine on Mortality and Efficacy
PROMISE: Prospective Randomised Milrinone Survival Evaluation
SOLVD-T: Studies of Left Ventricular Dysfunction Treatment

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Table 3 Design and conduct of β blocker heart failure trials

	USCP	CIBIS II	MERIT-HF
Estimated annual mortality in placebo group (%)	12.0	11.2	9.4
Estimated risk reduction with β blocker (%)	N/A*	25	30
Estimated duration of trial (years)			
Recruitment	–	1	1.2
Follow up	–	2	2.5
Estimated number of patients required	1101	2500	3500
Power of study to detect pre-specified risk reduction (%)	N/A†	95	80
Early stopping rules for benefit (significance level)?	No	Yes ($p < 0.001$)	Yes ($p < 0.0036$)
Recruitment started	23 April 1993	27 November 1995	14 February 1997
Recruitment stopped	N/A‡	13 May 1997	14 April 1998
Study programme stopped prematurely	Yes	Yes	Yes
Date study stopped	3 February 1995	5 March 1998	31 October 1998

*Trial designed to exclude a 33% increase in mortality; †95% power to detect a 33% increase in mortality; ‡some component studies still recruiting at time USCP terminated.

*Table 4 Inclusion criteria for β blocker heart failure trials**

	USCP	CIBIS II	MERIT-HF
Age (years)	18–85	18–80	40–80
NYHA class	II–IV	III–IV	II–IV
Duration of CHF (months)	3	3	3
Stability (weeks)	4	2	2
Diuretic	Required	Required	Required
ACE inhibitor	Required	Required	Required
Digoxin	Optional	Optional	Optional
Calcium antagonists	None	None†	Rate limiting excluded
Antiarrhythmic drugs	Classes Ic and III excluded‡	Only amiodarone permitted	Amiodarone excluded
LVEF	≤0.35	≤0.35	≤0.40
6 minute walk	All (various criteria)	Not done	< 450 m if LVEF 0.36–0.40
Heart rate (beats/min)	68	60	68
Systolic blood pressure (mm Hg)	85	100	100
Tolerability of β blocker (open label run in)	Required	Not required	Not required
Target dose (mg)	25/50 mg bid§	10 mg od	200 mg od¶

*All enrolled men and women; †2% in both treatment groups received dihydropyridines; ‡class III includes amiodarone; §50 mg bid for patients ⩾ 85 kg; ¶slow release formulation of metoprolol CR/XL.

Table 5 Characteristics of patients enrolled, end points, and annual mortality rates in the large β blocker trials in CHF

	USCP	CIBIS II	MERIT-HF
Number of patients	1094	2647	3991
Mean age (years)	58	61	64
Male sex (%)	77	81	78
Mean LVEF (%)	23	28	28
Ischaemic heart disease*	47	50	65
NYHA class (%)			
II	53	0	41
III	44	83	56
IV	3	17	3.6
Mean systolic BP (mm Hg)	115	130	130
Mean diastolic BP (mm Hg)	73	80	78
Mean heart rate (beats/min)	83	81	82
Atrial fibrillation	–	20	17
Diabetes mellitus	–	–	25
Hypertension	–	–	44
Primary end point	Various	Mortality	Mortality
Total number of deaths	54	384	362
Annual mortality rate†			
Placebo	N/A‡	13.2	11.0
β blocker	N/A	8.8	7.2
Mean follow up§	6.5 months	1.3 years	1 years

*Strict criteria were used to diagnose ischaemic heart disease in CIBIS II; †estimated annual mortality rate in CIBIS-II and mortality rate per patient year in MERIT-HF; ‡median follow up only 6.5 months; §median in case of USCP.

Table 6 β blocker heart failure trials: concomitant medication

	USCP	CIBIS II*	MERIT-HF
Diuretic	95†	99	91
ACE inhibitor	95	96	90‡
Digoxin	91	52	64
Aspirin/antiplatelet agent§	–	41§	46
Nitrates/direct acting vasodilators¶	32¶	58	–

*CIBIS II permitted amiodarone (which the other two trials did not)—15% received this drug; †loop diuretic; ‡96% ACE inhibitor or angiotensin II receptor antagonist; §antiplatelet agents in CIBIS II; ¶direct acting vasodilators in USCP.

Selection of patients for the USCP trials also differed in one other important way from CIBIS II and MERIT-HF. All patients in the USCP undertook a baseline exercise test and this was used to determine which component trial the patient entered (fig 1).

Twice as many patients were randomised to carvedilol as placebo.

PATIENT DETAILS

The total number of patients recruited in the USCP was much smaller than in the other two trials (table 3). They also differed from those in the other trials in a number of ways. Their mean age was only 58 years. The average left ventricular ejection fraction (LVEF) of patients in the USCP was considerably (5 percentage points) lower than in CIBIS II and MERIT-HF. Similarly, mean systolic blood pressure was 15 mm Hg lower than in the other two trials. Overall, this suggests the USCP patients should have been sicker, higher risk patients, yet more were categorised as New York Heart Association (NYHA) class II patients than in the other trials (see "event rates" below). A much higher proportion (30–40% more) of USCP patients received digoxin than in CIBIS II or MERIT-HF. The significance of this difference is unclear but it could be important and has been generally overlooked.

EVENT RATES

It is very difficult to compare event rates in the USCP trials to those in CIBIS II and MERIT-HF because of the very short (median

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Table 7 Deaths in the large β blocker mortality analyses

	USCP		*CIBIS II*		*MERIT-HF*	
	Placebo (n = 398)	*Carvedilol (n = 696)*	*Placebo (n = 1320)*	*Bisoprolol (n = 1327)*	*Placebo (n = 2001)*	*Metoprolol (n = 1990)*
All	31	22	228	156	217	145
Cardiovascular (%)*	31 (100)	20 (91)	161 (71)	119 (76)	203 (94)	128 (88)
Sudden (%)†	15 (48)	12 (55)	83 (36)	48 (31)	132 (61)	79 (54)
Pump failure§ (%)‡	13 (42)	5 (23)	47 (21)	36 (23)	58 (27)	30 (21)

*CIBIS II hazard ratio 0.71, 95% CI 0.56 to 0.90, p = 0.0049; MERIT-HF relative risk 0.62, 95% CI 0.50 to 0.78, p = 0.0003.
†CIBIS II hazard ratio 0.56, 95% CI 0.39 to 0.80, p = 0.0011; MERIT-HF relative risk 0.45, 95% CI 0.45 to 0.78, p = 0.0002.
‡CIBIS II hazard ratio 0.74, 95% CI 0.48 to 1.14, p = 0.17; MERIT-HF relative risk 0.51, 95% CI 0.33 to 0.79, p = 0.0023.
§Pump failure equates to progressive or worsening heart failure.

6.5 months) follow up in the USCP and the very small number of events in the USCP (tables 5 and 7). The reported placebo group mortality at six months was 7.8% and the survival curves suggest an annual mortality rate of 10–11%—that is, approaching that of MERIT-HF. The event rates in USCP do, however, seem similar to those in comparable previous trials. The six month mortality rate in the enalapril group of the studies of left ventricular dysfunction treatment (SOLVD-T) trial was 7.1%; the rate at one year was 12.3%.[10] The six month mortality rate in NETWORK was, however, only 3.5% and the one year rate in the captopril group of the evaluation of losartan in the elderly (ELITE I) trial, which randomised elderly patients, was 8.7%.[11 12]

In the placebo group of the USCP, 19.6% of patients had at least one hospitalisation for a cardiovascular reason; the proportion hospitalised for any reason was 27% and for heart failure it was 9%. The proportions in ELITE I admitted for any reason and for heart failure were 22.2% and 5.7%, respectively. The proportion of NETWORK patients requiring hospitalisation related to heart failure was 5.1%.[11 12]

Overall these comparisons suggest that the patients randomised into the USCP were at the sicker end of the NYHA class II–III spectrum.

Table 8 Treatment dosing in the large β blocker mortality analyses

	USCP	*CIBIS II*	*MERIT-HF*
Proportion of patients reaching target dose in β blocker group (%)	80	43	64
Proportion of patients reaching half or more of target dose (%)	–	67	87
Mean dose in β blocker group (mg)	45	–	159
Proportion stopping treatment early (%)			
Placebo	18	15	15.3
β blocker	11	15	13.9

Table 9 Adverse event rates in the USCP trials and CIBIS II

	*USCP**		*CIBIS II†*	
	Placebo	*Carvedilol*	*Placebo*	*Bisoprolol*
Heart failure	21	16	23	18
Dyspnoea	25	22	17	14
Dizziness	20	33	10	13
Bradycardia	1	9	5	15
Hypotension	4	9	7	11
Fatigue	23	25	7	9

*Reported by 5% or more of patients (also cardiomyopathy, tachycardia, viral infection and pneumonia); †most frequent adverse reactions.

FOLLOW UP

As already stated, the average follow up in the USCP was the shortest of the major β blocker mortality analyses (table 5). This has implications for interpreting the risk reduction associated with carvedilol; treatment effect is exaggerated by shorter follow up (see below). No patient was lost to mortality follow up.

HAEMODYNAMIC EFFECTS

These appeared similar to those reported in CIBIS II (see below), especially in relation to heart rate and blood pressure. Even though dizziness was a common complaint, mean blood pressure was not different between the placebo and carvedilol groups.

EFFECTS ON PRIMARY END POINTS OF COMPONENT TRIALS IN USCP

Though this review focuses on the mortality of the pooled USCP trials, the component trials each had primary and secondary prespecified end points.[2–5] These are listed in tables 1 and 2.

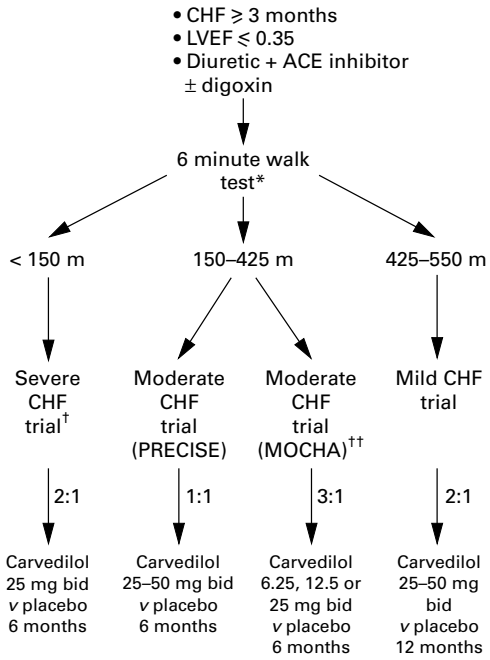

*Figure 1 Design of the USCP trials in CHF. *Qualifying six minute walk distances modified during study: for severe CHF trial changed to < 350 m; for PRECISE upper limit changed to 450 m; for MOCHA upper limit changed to 450 m; for mild CHF trial upper limit changed to 450 m. †Neither enrolment nor follow up completed by time US carvedilol programme stopped. ††Dose response study.*

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The ability of the individual trials to show a benefit of carvedilol was reduced by early termination of the US programme, such that recruitment and/or follow up was incomplete in some of the component trials. In retrospect, it is also probably the case that exercise testing, a measure of treatment efficacy still in vogue at the time of the design of the USCP, was not a good end point to choose to measure the effect of a β blocker. Despite this carvedilol improved the primary end point, progression of heart failure, in the "mild" trial.[2] One of the two primary exercise end points in the "moderate" prospective randomised evaluation of carvedilol on symptoms and exercise (PRECISE) trial was also significantly improved. In addition, many of the secondary end points were improved by active treatment (table 2).[3]

EFFECTS ON MORTALITY

Carvedilol reduced total mortality by 65% (95% confidence interval (CI) 39% to 80%)—that is, from 7.8% to 3.2% (31/398 placebo deaths *v* 22/696 carvedilol deaths), a highly significant effect ($p < 0.001$).[1] Superficially, this seems a much larger average effect than that seen in either CIBIS II, where there was a 34% reduction (95% CI 19% to 46%), or MERIT-HF, where the reduction was also 34% (95% CI 19% to 47%). Of course, it is immediately apparent that the CIs around these average reductions overlap. Furthermore, the larger sample size in CIBIS II and MERIT-HF (2647 and 3991 *v* 1094) and larger number of events (384 and 362 deaths in CIBIS II and MERIT-HF, respectively, compared to 54 in the USCP trials) means that the estimated risk reduction in CIBIS II and MERIT-HF is more robust and more likely to represent the "real" effect of β blockade in these patients.

There are two other important issues to take into consideration when looking at the apparently large mortality risk reduction in the USCP. The first is the confounding effect of the open label run-in period. At the time of termination of the USCP, 1197 patients had entered the open label run in period. Of these, 5.6% had failed to complete the period because of adverse effects (including worsening heart failure in 1.4% and death in 0.6%). A further 3.0% failed to do so because of violations of the protocol or other administrative reasons. In CIBIS II and MERIT-HF, patients not tolerating study drug, experiencing early adverse effects, not adhering to treatment, or having events such as death or worsening heart failure were counted in the intention to treat analysis from day 1 (as there was no prerandomisation run-in period to exclude such participants). It is difficult to know how to deal with this bias in favour of carvedilol. One way is to add all events occurring in the run-in period to the carvedilol group in the USCP.[13–15] Though this is a fairly harsh approach it does not substantially alter the overall conclusion from the USCP (the mortality risk reduction is a little less at 48% but still significant at $p = 0.011$).[14 15]

Another approach has been to carry out this "worst case" analysis and, in addition, pool the results of the USCP with those of another large carvedilol heart failure trial (the Australia-New Zealand trial). The Australia-New Zealand trial (208 placebo and 207 carvedilol treated patients) did not show a reduction in mortality after an average follow up of 19 months (26 placebo deaths *v* 20 carvedilol deaths, relative risk 0.76, 95% CI 0.42 to 1.36, $2p > 0.1$).[16] This pooling gives an estimated relative risk of death with carvedilol, versus placebo, of 0.55 (95% CI 0.325 to 0.924)—that is, a 45% reduction in mortality with carvedilol.[17]

The second important issue affecting the interpretation of the size of the mortality reduction in the USCP is that of duration of follow up. Short term follow up can exaggerate, and long term follow up diminish, the effect of treatment. Take, for example, the SOLVD-T trial.[10] The mortality risk reduction at three, six, and 12 months was 33%, 29%, and 23% compared to 16% during the overall follow up of 41.4 months. It is quite likely, therefore, that the short follow up in the USCP has exaggerated the benefit of carvedilol; this is also generally true of all the β blocker trials (duration 0.5–1.3 years) compared to the landmark angiotensin converting enzyme (ACE) inhibitor trial, SOLVD-T.

Sudden death was reduced substantially in the USCP trials, as in the other trials (table 7). Also in keeping with the other trials, the mortality benefit from carvedilol was seen across a wide range of subgroups.

EFFECT OF CARVEDILOL ON MORBIDITY

Carvedilol reduced the proportion of patients requiring at least one hospitalisation for a cardiovascular cause: 19.6% in the placebo group and 14.1% in the carvedilol group, a 27% (95% CI 3% to 45%) risk reduction ($p = 0.036$).[1 15] The proportions admitted for any cause (27% *v* 19%) and for worsening CHF (9% *v* 6%) were also reduced significantly ($p = 0.009$ and $p = 0.041$, respectively). The combined end point of death or hospitalisation for a cardiovascular reason was reduced from 24.6% in the placebo group to 15.8% in the carvedilol group, a 38% risk reduction (95% CI 18% to 53%, $p < 0.001$). The same end point was reduced from 35% to 29% in CIBIS II, a risk reduction of 21% (95% CI 10% to 31%, $p = 0.0004$).

DOSING

The target dose of carvedilol in the USCP was 25 mg twice daily (50 mg twice daily in patients ⩾ 85 kg). A very high percentage of patients appeared to reach target dose in the USCP trials, though it must be remembered that this proportion will have been inflated by exclusion of intolerant patients during the open label run-in period (table 8).[1]

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TOLERABILITY AND ADVERSE EFFECTS

The main results paper of the USCP mortality analysis only describes permanent discontinuations because of adverse reactions (compared with CIBIS II and MERIT-HF, which describe overall discontinuation rates)[1 7 9]; 7.8% of the placebo group and 5.7% of the carvedilol group in the USCP stopped treatment because of adverse reactions. Analysis of the reports of the individual component trials of the USCP,[2–5] however, gives overall discontinuation rates of 18.3% in the placebo group and 10.8% in the carvedilol group, proportions very similar to CIBIS II (15% in both treatment groups) and MERIT-HF (15.3% in the placebo group and 13.9% in the metoprolol group). It is very difficult, however, to compare adverse event rates and discontinuation rates in the USCP to the other trials because of the exclusion of carvedilol intolerant patients during the open label run-in phase.

With this caveat in mind, the overall rates of adverse reactions in the USCP are shown in table 9, which also shows the comparable rates reported for CIBIS II (these data are not available for MERIT-HF). The rates are broadly similar with the exception of dizziness which seems to be more common with carvedilol, possibly because of its α adrenoceptor antagonist action.

The main report of the USCP mortality analysis and the reports of the individual component trials give a great deal more interesting information on adverse events.[1–5] These data detail adverse events during initiation, up titration, and maintenance, allow comparison between adverse event rates in patients with milder CHF and in those with more severe CHF, and permit comparison of lower and higher dose carvedilol treatment. The most common adverse events leading to discontinuation of double blind treatment are also described. A thorough review of these data is beyond the scope of this review though some general points can be made. Dizziness seemed to be the most common adverse event reported during treatment initiation (in around 13–15% of patients in the open label challenge phase). Worsening CHF appeared to occur a bit more commonly in more severe patients (7.3% in moderately severe *v* 4.0% in mild) during the open label challenge phase with carvedilol and withdrawals were common in patients with more severe CHF during this phase (8.0% *v* 5.9%). Worsening heart failure was a bit more common in the carvedilol group, than in the placebo group, during the up titration phase but this effect was reversed during maintenance treatment—that is, worsening CHF was seen more commonly in the placebo group during this later phase.

The unique design of the USCP, in having an open label run-in period, also allows comparison between the adverse events related to initiation of an ACE inhibitor and a β blocker. The SOLVD trials also had an open label enalapril run-in period.[10] The median duration of the open label challenge in the SOLVD trials was seven days, and 98/7487 (1.3%) of patients had to stop treatment because of an adverse effect (2.6% of NYHA class III/IV patients). The duration of the open label phase of the USCP was 14 days, and 67/1197 (5.6%) of patients had to stop treatment. Fifteen per cent of patients with mild CHF and 13.6% of patients with moderately severe CHF reported dizziness in the USCP versus 6.4% in SOLVD-T. Adverse effects from carvedilol are, therefore, probably a bit more common than with an ACE inhibitor.

CIBIS II

Details of CIBIS II, which recruited in Europe, are given in tables 3–9.[6–7]

AIM OF STUDY

The primary objective of CIBIS II was to examine the effect of bisoprolol, added to conventional treatment, on all cause mortality in patients with moderate to severe symptomatic chronic heart failure caused by reduced left ventricular systolic function (table 3).

ENTRY CRITERIA

The major difference between the entry criteria for CIBIS II, MERIT-HF, and the USCP was NYHA class (tables 3 and 4).[1–9] This should have resulted in CIBIS II having a higher mortality rate than the other trials (see below). MERIT-HF and the USCP recruited patients with NYHA class II–IV CHF whereas CIBIS II sought class III and IV patients only. Patients entering CIBIS II could be treated with amiodarone whereas concomitant treatment with this antiarrhythmic agent was excluded by the other trials.[1–9]

PATIENT DETAILS

Apart from the distribution of NYHA class, the characteristics of the patients in CIBIS II were very similar to those in MERIT-HF and quite similar to those in the USCP trials (tables 5 and 6).

EVENT RATES

CIBIS II had more deaths than any of the other trials (seven times as many as the USCP; tables 5 and 7).[7] The annual mortality rate of 13.2% in the placebo group (17.3% over the whole follow up period) was a little higher than in MERIT-HF and similar to that in NYHA class III and IV patients in MERIT-HF. The placebo group mortality rates in class III and IV patients were 15.8% and 24.6% in CIBIS II and 13.2% and 24.9% in MERIT-HF; the average follow up was, however, longer in CIBIS II than MERIT-HF (see below). These mortality rates are lower than in other recent trials recruiting class III and IV patients. Placebo group mortality was: 24% (after a mean follow up of 6.1 months) in the prospective randomised milrinone survival evaluation (PROMISE) study[18]; 38% (over 13.8 months) in the prospective randomised amlodipine survival evaluation (PRAISE) study[19]; 20% (over 12 months) in the second prospective randomised study of ibopamine on mortality and efficacy (PRIME 2)[20]; and 19% (over nine

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months) in the vesnarinone CHF mortality study.[21] By contrast, the one year mortality rate in SOLVD-T (57% NYHA class II) was 12.3%.[10]

The proportion of patients dying suddenly seemed to be considerably smaller in CIBIS II than MERIT-HF (table 7). This may reflect a different end point classification system and/or the higher proportion of patients with more severe CHF who are more likely to die from pump failure than suddenly.[9]

The main CIBIS II results paper gives much more information on morbidity than either of the other two trial reports.[7] The proportion of patients hospitalised in the placebo (diuretic, ACE inhibitor and/or digoxin) group was 39% for any cause and 18% for worsening CHF; the proportion dying or being hospitalised, for a cardiovascular reason, was 35%. These rates also seem a little low for true NYHA class III/IV patients. In the PRIME 2 study the proportion of patients in the placebo group hospitalised during a mean follow up of one year was 44%.[20] In the vesnarinone CHF mortality study the proportion of patients hospitalised for worsening CHF, during a mean follow up of nine months, was 18.5%; in this study the proportion dying or requiring hospitalisation for CHF was 29.8%.[21] In the digoxin investigation group (DIG) trial (where 54% of patients were NYHA class II) the one year rate of death or hospitalisation for any reason was 41% in the digoxin group; the rate for cardiovascular death or cardiovascular hospitalisation was 32%.[22]

FOLLOW UP

The average follow up in CIBIS II (1.3 years) was the longest of the major β blocker trials. Six patients (five in the bisoprolol group) were lost to follow up.[7]

HAEMODYNAMIC EFFECTS

No haemodynamic effects are reported in the main results paper from CIBIS II.[7]

EFFECTS ON MORTALITY

Bisoprolol reduced total mortality by 34%.[7] The total number of deaths was 228 (17.3%) in the placebo group and 156 (11.8%) in the bisoprolol group ($p < 0.0001$). The estimated annual mortality rate was 13.2% in the placebo group and 8.8% in the bisoprolol group (hazard ratio 0.66, 95% CI 0.54 to 0.81). Sudden death was reduced by 44% in the bisoprolol group (table 7). This mortality benefit was seen across a wide range of subgroups.

EFFECT OF BISOPROLOL ON MORBIDITY

Bisoprolol had a striking effect on cardiovascular morbidity as well as mortality.[7] Significantly fewer bisoprolol patients (33%) than placebo patients (39%) required a hospital admission (hazard ratio 0.80, 95% CI 0.71 to 0.91, $p = 0.0006$). Hospital admission for worsening heart failure was also significantly less common in the bisoprolol group (12% of patients) than in the placebo group (18%) (hazard ratio 0.64, 95% CI 0.53 to 0.79, $p = 0.0001$). There were also fewer hospital admissions for ventricular arrhythmias (6 *v* 20, $p = 0.006$) and hypotension (3 *v* 11, $p = 0.03$). There were, however, more admissions in the bisoprolol group for stroke (31 *v* 16, $p = 0.04$) and bradycardia (14 *v* 2, $p < 0.004$). There was no difference between the groups for other types of hospital admission.

DOSING

The proportion of patients reaching target dose (10 mg), or half target dose, was lower in CIBIS II than in the other studies (table 8). Why this should be is not clear. One possibility, however, is that CIBIS II recruited sicker patients (more NYHA class III and IV) than the other trials and these patients may have been less able to tolerate larger β blocker doses (see USCP adverse events, above). The proportion reaching target dose in the USCP will have been exaggerated by the programme design (open label run-in). Even so, the proportion of patients reaching target dose in CIBIS II is still lower than in MERIT-HF.

TOLERABILITY AND ADVERSE EFFECTS

The proportion of patients discontinuing study drug was the same in the placebo and active treatment groups (15%) and was similar to that in MERIT-HF.[7] The placebo corrected rates of adverse events in CIBIS II were very similar to those reported in the USCP trials with the exception of dizziness (3% excess in CIBIS II, 13% excess in the USCP; table 9). This difference may reflect the α blocking action of carvedilol. The main MERIT-HF results paper does not report adverse events.[9]

MERIT-HF

Details of MERIT-HF, which recruited in Europe and North America, are given in tables 3–8.[8 9]

AIM OF STUDY

The primary objective of MERIT-HF was to examine the effect of metoprolol, added to conventional treatment, on all cause mortality in patients with moderately severe symptomatic chronic heart failure caused by reduced left ventricular systolic function.[8 9]

ENTRY CRITERIA

The enrolment criteria were very similar to those in CIBIS II and the USCP (tables 3 and 4).[8 9] There were only three notable differences. Patients with higher LVEF (≤ 0.40 *v* < 0.35) could be enrolled in MERIT-HF, but only if they had a reduced exercise capacity. While CIBIS II recruited NYHA class III and IV patients, MERIT-HF could recruit NYHA class II–IV patients. Patients in MERIT-HF were also required to have a higher resting heart rate than those in CIBIS II (≥ 68 *v* ≥ 60 beats/minute). Patients were enrolled after a two week, single blind, placebo period.

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PATIENT DETAILS

MERIT-HF actually recruited the largest number of patients of the three trials. The average age of patients was older than in the other trials, and MERIT-HF recruited a smaller proportion of NYHA class III (and a greater proportion of class II) patients, by design, than CIBIS II (tables 5 and 6). Blood pressure, heart rate, and LVEF were similar to CIBIS II, as was concomitant medical treatment.

EVENT RATES

In keeping with the broader enrolment criteria in MERIT-HF (class II–IV *v* class III–IV and higher LVEF), annual mortality was a little lower than in CIBIS II (11.0% *v* 13.2%, table 5).[7 9] In the placebo group, the mortality rate in NYHA class II, III, and IV patients was 7.1%, 13.2%, and 24.9% per patient year of follow up, respectively. The corresponding rates in class III and IV patients in CIBIS II were very similar at 15.8% and 24.6%. The proportion of patients dying suddenly in MERIT-HF was greater than in CIBIS II (61% *v* 36% in the respective placebo groups), in keeping with the higher proportion of NYHA class II patients (patients with milder heart failure are more likely to die suddenly whereas those with more severe heart failure are more likely to die from progressive pump failure) (table 7).[7 9]

FOLLOW UP

Average follow up in MERIT-HF was slightly shorter than in CIBIS II (1.0 *v* 1.3 years).[7 9] No patients were lost to follow up.

HAEMODYNAMIC EFFECTS

After six months, heart rate fell by 3 beats/minute in the placebo group compared to 14 beats/minute in the metoprolol group ($p < 0.0001$).[9] This was very similar to the changes in heart rate in the USCP (a reduction of 1.4 and 12.6 beats/minute in the placebo and carvedilol groups, respectively; $p < 0.001$).[1] Remarkably, there was a smaller reduction in systolic blood pressure in the metoprolol group (−2.1 mm Hg) than in the placebo group (−3.5 mm Hg; $p = 0.013$). Blood pressure did not change significantly in either treatment group in the USCP.[1]

EFFECTS ON MORTALITY

Metoprolol reduced total mortality by 34% (relative risk 0.66, 95% CI 0.53 to 0.81), a treatment effect identical to that of bisoprolol in CIBIS II.[7 9] Metoprolol also had a broadly similar effect to bisoprolol on specific causes and modes of death (table 7). In particular, the risk of sudden death was substantially reduced. The mortality benefit was seen across a wide range of patient subgroups.[9]

EFFECTS ON MORBIDITY

Hospitalisation and other morbidities are not reported in the principal MERIT-HF results paper.

DOSING

The target dose of slow release metoprolol in MERIT-HF was 200 mg once daily.[9] The mean dose achieved in the active treatment group was 159 mg compared to 179 mg in the placebo group (table 8). Sixty four per cent of metoprolol treated patients and 82% of placebo treated patients reached the target dose; 91% of the placebo group and 87% of the metoprolol group were titrated to a maintenance dose of 100 mg or more (half target dose). The proportion of patients reaching higher maintenance doses was greater than in CIBIS II but smaller than in the USCP (table 8).[1 7 9] The design of the USCP, with an open label run-in period, will, however, almost certainly have inflated the proportion reaching target in the carvedilol studies.

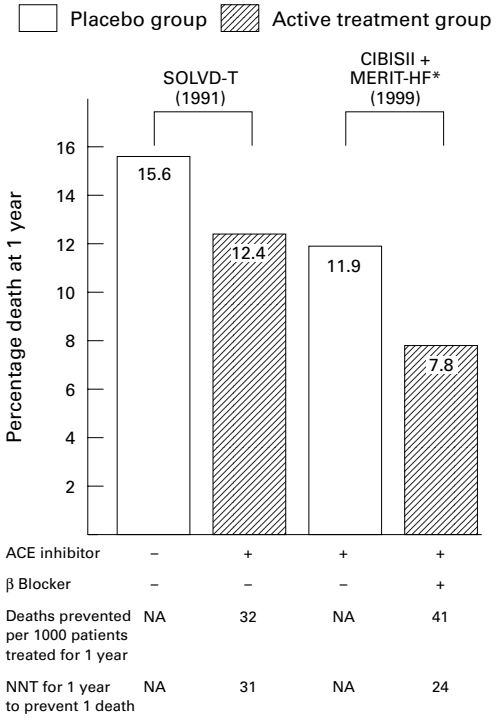

*Figure 2 Mortality benefit of β blockers and ACE inhibitors in CHF trials. *Annual mortality from pooled CIBIS II and MERIT-HF; +, treatment given; −, treatment not given; NA, not applicable (a placebo reference group); NNT, number needed to treat.*

TOLERABILITY AND ADVERSE EFFECTS

The principal MERIT-HF results paper reports that study drug was permanently discontinued early in 15.3% of the placebo group and 13.9% of the metoprolol group (relative risk 0.90, 95% CI 0.77 to 1.06). This is very similar to the proportion of patients stopping treatment prematurely in CIBIS II (15% in both treatment groups).[7] Adverse effects are not reported in the principal MERIT-HF results paper.[9]

Table 10 Pooled analysis of mortality in NYHA class III and IV patients in USCP, CIBIS II, and MERIT-HF

NYHA class	*Placebo (mortality)*	*β Blocker (mortality)*
III	334/2373 (14.1%)	217/2519 (8.6%)
IV	71/313 (22.7%)	53/309 (17.5%)

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*Table 11 Initiating dose, target dose, and titration scheme of β blocking agents in placebo controlled large trials**

β Blocker	First dose (mg)	Titration scheme daily dose (mg)†									Target total daily dose (mg)
Metoprolol (MERIT trial)	25‡	Wk 1 25	Wk 2 25	Wk 3 50	Wk 4 50	Wk 5 100	Wk 6 100	Wk 7 200			200
Bisoprolol (CIBIS II)	1.25	Wk 1 1.25	Wk 2 2.5	Wk 3 3.75	Wk 4–7 5.0				Wk 8–11 7.5	Wk 12–15 10	10
Carvedilol§ (US trials)	3.125	Wk 1 3.125	Wk 2 3.125	Wk 3 6.25	Wk 4 6.25	Wk 5 12.5	Wk 6 12.5	Wk 7 25	Wk 8 25		50¶

*Forced titration in all studies, assuming preceding dose tolerated.
†Dose once daily for metoprolol and bisoprolol and twice daily for carvedilol.
‡Slow release (metoprolol CR/XL) formulation 12.5 mg recommended in NYHA class III–IV patients.
§Recommended titration schedule in UK; in USCP dosing schedule differed in different component trials.
¶In two doses: 25 mg bid except for patients > 85 kg where the dose may be increased to 50 mg bid.

What we still do not know about β blockers in CHF

The trials, to date, have randomised mainly stable NYHA class II–III CHF patients. The proportion of class IV patients is small and the benefit in these patients uncertain (table 10). That the class IV patients in CIBIS II had a relatively low event rate (may not have been "true" class IV patients) adds to this uncertainty. The β blocker evaluation trial (BEST), with more severe patients than CIBIS II, has recently stopped.[23] BEST failed to show a clear cut benefit of treatment in those sicker patients (placebo mortality 16%, bucindilol mortality 14%). The ongoing COPERNICUS trial will hopefully clear up any doubt about patients with severe CHF.[15]

All three trials recruited relatively young patients, though subgroup analyses of MERIT-HF and the USCP suggests that benefit is obtained in both younger and older patients.[1 7 9] Similarly, all three trials recruited few female patients (about 20% in total). Because of this there is some uncertainty about the benefit in women. The USCP suggests a greater benefit in women than men (though the numbers are extremely small).[1] MERIT-HF shows a trend in the opposite direction.[9] The main CIBIS II report does not give a breakdown of results by sex.[7] Formal meta-analysis should shed more light on this issue.

We also clearly do not know about giving β blocker treatment to less stable patients and about more rapid treatment titration schedules. To date there is no good evidence to show that one β blocker is more efficacious or better tolerated than another although the COMET trial, comparing short acting metoprolol to carvedilol, may shed some light on this.

Conclusions

It seems quite clear from the totality of the data presented that β blockers substantially reduce mortality and morbidity in patients with stable NYHA class II and III CHF caused by left ventricular systolic dysfunction of all causes.[1 7 9] These large trials are supported by meta-analyses of smaller studies.[24–28] The mortality benefit is probably a little larger than that obtained with ACE inhibitors (but is incremental to ACE inhibitor benefit; fig 2). On the whole, initiated at a low dose and titrated slowly, β blockers are well tolerated in CHF though perhaps a little less well than ACE inhibitors.

The totality of evidence shows that all stable NYHA class II–III CHF patients with reduced left ventricular systolic function should receive a β blocker, in addition to standard treatment (including an ACE inhibitor), unless there is a specific contraindication (for example, asthma). Treatment should be used according to the dosing regimen and titration protocol used in one of the three large mortality studies (table 11).

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