

## REVIEW

# $\beta$ -blockers in left ventricular systolic dysfunction—from evidence to practice

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## Abstract

Five percent of all hospital medical admissions are patients with heart failure. The incidence is about one new case per 1000 of the general population per year, increasing to >10 per 1000 in those aged  $\geq 85$  years. Although the evidence that  $\beta$ -blockers reduce mortality by about 36% when added to angiotensin-converting enzyme inhibitors is overwhelming, clinicians are still reluctant to use  $\beta$ -blockers in heart failure, especially in older patients. Here, we examine the evidence for the use of  $\beta$ -blockers in heart failure in older people and explore the practicalities of their use.

**Keywords:**  $\beta$ -blockers, heart failure

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## Introduction

Heart failure is common, with a prevalence of 3.9% in those aged over 55 years [1] and 8% in those aged over 75 [2]. The incidence of new cases is highest (11.6 per 1000) in those aged >85, with a median age of 76 years for first presentation in the United Kingdom [3]. Heart failure accounts for about 5% of hospital medical admissions in the UK, with high readmission rates (about 50% in 3 months [4]). Despite many recent advances in treatment, the prognosis of heart failure in the community has not improved greatly [5].

Although there is substantial evidence that when  $\beta$ -blockers are added to angiotensin-converting enzyme inhibitors they reduce mortality by 36% [6], clinicians are still reluctant to use them in heart failure, especially in older patients. The OSCUR study [7] found significant differences in the prescribing of  $\beta$ -blockers in heart failure between cardiologists (41%) and physicians (4%). An accompanying editorial in the *European Heart Journal* challenges all of us looking after patients with heart failure to initiate  $\beta$ -blocker treatment [8].

Here, we examine the evidence for  $\beta$ -blockers in the management of heart failure (especially in older people) and explore the practicalities of their use.

## Representation of older people in $\beta$ -blocker trials

We carried out a computerized search of the MEDLINE database for the last 20 years to identify randomized controlled trials of  $\beta$ -blockers in heart failure published in English. The inclusion criteria were being a randomized placebo-controlled trial of oral  $\beta$ -blocker therapy in patients with heart failure and having mortality and/or morbidity (hospitalization due to worsening heart failure) and/or changes in functional status—assessed by the New York Heart Association (NYHA) classification—as outcome measures.

We scrutinized those trials meeting our eligibility criteria to identify the mean age, age range and sex of patients enrolled, and calculated the mean age and sex distribution of the pooled trial populations.

We identified 27 trials [9–36]. In total, 13 070 patients were randomized, 10 264 (79%) of whom were men. The mean age was 60.3 years. Five trials enrolled up to the age of 70 years, five up to 75 years, five up to 80 years and two up to 85 years. The age range was not available for 10. Seven trials were powered for mortality as a single or composite end-point. These trials are summarized in Table 1.

Table I. Major clinical trials of  $\beta$ -blockers

Drug	Trial	Patients included		Age, years			Significant outcome/benefit
		NYHA class	n	Mean	Range	Male : female	
Bisoprolol	CIBIS I [25]	III/IV	641	60	18–75	83 : 17	Improved symptoms (functional state)
	CIBIS II [12]	III (83%); IV (17%)	2647	61	26–80	81 : 19	34% reduction in mortality
Carvedilol	US Carvedilol [10]	II–IV	1094	57.9	18–85	76 : 24	65% reduction in mortality
	Australia-NZ [13]	II/III	415	67	–	80 : 20	26% reduction in mortality and hospital admissions
Metoprolol	COPERNICUS [36]	IV	2289	63.2	–	79 : 21	35% improvement in mortality
	MDC [14]	II/III	383	49	16–71	70 : 30	Improved left ventricular function and symptoms
	MERIT-HF [9]	II–IV: 41% II; 56% III	3991	63.9	40–80	77 : 23	34% improvement in survival

NYHA, New York Heart Association.

Australia-NZ, Australia/New Zealand Heart Failure Research Collaborative Group Study; CIBIS, Cardiac Insufficiency Bisoprolol Study; COPERNICUS, Carvedilol Prospective Randomised Cumulative Survival Study; MERIT-HF, Metoprolol Randomised Intervention Trial in Congestive Heart Failure; MDC, Metoprolol in Dilated Cardiomyopathy Study.

Of the randomized controlled trials powered for mortality, the Metoprolol Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) [9] enrolled 1245 subjects (32%) aged between 70 and 80 years, and demonstrated a significant reduction in mortality in this age group. A *post hoc* analysis of the second Cardiac Insufficiency Bisoprolol Study (CIBIS II) [12] presented at the European Cardiac Society Working Group on Heart Failure Meeting in Venice in 2000 showed similar mortality benefits in people aged 71–80 years and those 71 years (relative risks 0.68 for 71–80 years and 0.69 for <71 years). The Carvedilol Prospective Randomised Cumulative Survival study (COPERNICUS) demonstrated significant mortality reductions both in those under and those over 65 [36].

No significant reduction in mortality was seen in women in MERIT-HF. However, few women were enrolled, so the power was low. The US Carvedilol [10] trial did show significant mortality benefits in women.

The  $\beta$ -Blocker Evaluation Survival Trial (BEST) of bucindolol in heart failure [11] enrolled 23% black patients (compared with 5% in MERIT-HF and none in CIBIS II). A retrospective subgroup analysis showed a significant 20% reduction in mortality in white patients only. The effects of  $\beta$ -blockade in heart failure in different races needs further study.

### From evidence to practice—tolerability of $\beta$ -blockers in the trials

Of the many  $\beta$ -blockers available, three have been extensively evaluated in large-scale trials in patients with reduced ejection fraction and mild to moderate heart failure. They are carvedilol in the US Carvedilol programme [10] and Australia/New Zealand Heart Failure Research Collaborative Group Study [13], metoprolol in MERIT-HF [9] and bisoprolol in CIBIS-II [12]. In addition, COPERNICUS [36] evaluated carvedilol in

severe heart failure, defined as dyspnoea or fatigue at rest or on minimal exertion for at least 2 months and an ejection fraction of <25%.

In all of these trials,  $\beta$ -blockers were introduced only after left ventricular systolic dysfunction had been stabilized with conventional therapy including angiotensin-converting enzyme inhibitors, diuretics and/or digoxin. With the exception of COPERNICUS, the trials enrolled patients only if they had been diagnosed for at least 3 months and had been on stable treatment for at least 6 weeks. COPERNICUS allowed recent adjustment in medication, including the use of intravenous diuretics immediately before randomization.

The major overall contraindications to enrolment are shown in Table 2. Trials varied in how much pulmonary disease was excluded. Patients with chronic obstructive airways disease were excluded from the Australia/New Zealand study, while CIBIS II excluded those with airways reversibility.

### Carvedilol

In the US Carvedilol study, mortality was reduced by 65% and hospitalizations by 27% [10]. Patients were subjected to an 'open-label run-in' of 6.25 mg carvedilol twice a day for 2 weeks and patients intolerant of  $\beta$ -blockers were then excluded. Of 1197 patients in this open-label phase, 5.6% failed to continue due to intolerance of the drug. Eighty percent of patients reached the target carvedilol dose of 25/50 mg twice daily (depending on body weight), with only 11% stopping treatment early (compared with 18% of those taking placebo).

The Australia/New Zealand study of carvedilol [13] had a similar run-in phase. Of 442 patients in the run-in phase, 415 were randomized, with an initial withdrawal rate of only 6%. At the end of the study,

**Table 2.** Major trials of  $\beta$ -blockers: contraindications to use in

Heart rate < 60 beats/min (< 68 beats/min in US Carvedilol)
Systolic blood pressure < 100 mmHg (< 85 mmHg in US Carvedilol and COPERNICUS)
Higher-degree atrioventricular block (unless with an implanted pacemaker)
Decompensated heart failure (pulmonary oedema, hypotension, ascites, significant peripheral oedema)
Chronic obstructive airways disease or asthma
Significant renal impairment <sup>a</sup>
Known hypersensitivity to $\beta$ -blockers

<sup>a</sup>Defined as serum creatinine > 300  $\mu\text{mol/l}$  in CIBIS II, > 247.5  $\mu\text{mol/l}$  in COPERNICUS and > 250  $\mu\text{mol/l}$  in Australia/New Zealand Heart Failure Research Collaborative Group Study.

48% were on the target dose (50 mg/day) and withdrawal rates were 19% with treatment and 14% with placebo.

The recently reported COPERNICUS study [36] has reinforced the benefits and tolerability of carvedilol in severe heart failure. COPERNICUS was stopped early on the recommendation of the Data and Safety Monitoring Board, because of a significant 35% reduction in mortality. Sixty-five percent of patients achieved the target dose of 25 mg twice a day, while 15% of those on carvedilol and 18% of those on placebo were withdrawn because of adverse events. Although COPERNICUS enrolled patients with severe heart failure (including some hospitalized patients), the sickest elderly patients in this group—particularly those with hypotension, persistent sodium and water retention and severe renal impairment—were excluded.

### Metoprolol

In the MERIT-HF trial [9], 64% of patients reached the target dose of 200 mg/day, while 14% of those on metoprolol and 15% of those on placebo discontinued treatment early.

### Bisoprolol

In CIBIS-II, 43% of patients reached the target dose of 10 mg/day and 67% the half-target dose of 5 mg [12]. Fifteen percent of patients discontinued the drug. Bisoprolol reduced mortality by 34% and hospital admissions for worsening heart failure by 32%.

### Withdrawal and adverse effects

The withdrawal rate in all large-scale trials evaluating carvedilol, metoprolol and bisoprolol was about 15%. This was comparable to placebo withdrawal rates, suggesting that these drugs are well tolerated—at least in the trials.

However,  $\beta$ -blockers are less well tolerated in clinical practice. One study of 230 patients attending a heart failure and heart transplant assessment clinic reported adverse events with carvedilol in 43% of NYHA class IV patients and 24% NYHA class I–III patients, resulting in permanent withdrawal of the drug in 25% of patients from class IV and 13% of patients from classes I–III. Those with class IV heart failure were significantly older (mean age 57 years) than those with class I heart failure (mean age 45 years) [37].

In a small study of bisoprolol tolerability in patients with heart failure aged  $\geq 70$  years, Baxter *et al.* [38] reported clinically significant first-dose hypotension in 93%. Further data on the long-term tolerability of  $\beta$ -blockers in clinical practice in elderly heart failure patients are needed.

## From evidence to practice—how $\beta$ -blockers were used in the trials

So why were  $\beta$ -blockers so well tolerated in the trials and how were such target doses achieved?

First, with the exception of COPERNICUS, all trials enrolled stable chronic patients—i.e. those who were not on intravenous therapy, had not had changes in their treatment in the previous 2–4 weeks and were generally oedema-free. Thus, in addition to excluding patients with contraindications to  $\beta$ -blockers (asthma, hypotension, bradycardia etc), they also excluded patients whose heart failure was ‘unstable’. The patients in COPERNICUS were also oedema-free, but they were sicker with more severe heart failure and, unlike those in the other trials, some were in hospital at the time of enrolment.

Secondly, the essence of treatment in all of these trials was ‘start low and go slow’. (See Table 3 for a summary of the dosage regimens.)

Finally, patient monitoring in the trials was intense—particularly during the titration phase, when patients were seen every 1–2 weeks. Particular emphasis was placed on patient education and self-monitoring. Patients in the US Carvedilol programme were asked to weigh themselves daily and, if their weight was going up by 1–1.5 kg, increase their diuretics. If patients developed pulmonary oedema, the  $\beta$ -blockers were stopped for 2–3 days, and the pulmonary oedema treated before the  $\beta$ -blockers were reintroduced.

## Current service developments and the management of heart failure

Given the need for complicated dose titration of  $\beta$ -blockers, close monitoring and education of patients in self-management, older people with heart failure will need extra support if they are to benefit maximally from current therapeutic developments. Nurse-led

**Table 3.** Dosing regimens in trials of  $\beta$ -blockers

Drug	Trial	Dose, mg				
		Open-label run-in	After randomization	Up-titration	Target	Titration, weeks
Bisoprolol	CIBIS II [12]	None	1.25 once daily, 1 week	2.5, 3.75, 5, 7.5	10 <sup>a</sup>	15
Carvedilol	US Carvedilol [10]	6.25 twice daily, 2 weeks	6.25, 2 weeks	12.5	25 <sup>b</sup>	2–10
	Australia-NZ [13]	3.125 twice daily, 2 weeks	6.25, 1–2 weeks	6.25, 12.5	25 <sup>b</sup>	2–5
Metoprolol	COPERNICUS [36]	None	3.125 twice daily, 2 weeks	6.25, 12.5	25 <sup>b</sup>	8
	MERIT-HF [9]	Placebo run-in, 2 weeks	12.5 once daily, 2 weeks	25, 50, 100	200 <sup>a</sup>	8–10

<sup>a</sup>dosage per day.

<sup>b</sup>dosage twice daily.

Australia-NZ, Australia/New Zealand Heart Failure Research Collaborative Group Study; CIBIS, Cardiac Insufficiency Bisoprolol Study; COPERNICUS, Carvedilol Prospective Randomised Cumulative Survival Study; MERIT-HF, Metoprolol Randomised Intervention Trial in Congestive Heart Failure.

interventions in heart failure are being developed mainly in cardiology clinics rather than in care of the elderly clinics, where many older heart failure patients are to be found.

Even before the advent of  $\beta$ -blockers in heart failure, Rich *et al.* showed that multidisciplinary nurse-directed interventions, with an emphasis on patient education, reduced hospital readmissions for heart failure by 56.2% and improved compliance from 64.9–82.5% ( $P < 0.02$ ) in older patients with heart failure [39]. Since then, several other nurse-led multidisciplinary interventions in Australia and North America [40–42] have been shown to reduce hospital readmissions for heart failure. Although they are described as ‘multidisciplinary’, the main intervention in all these trials was a cardiac nurse whose work focused on patient education, optimization of medical treatment and early detection of decompensation.

A Scottish trial of specialist nurse intervention in 165 older hospitalized heart failure patients has also demonstrated that nurse intervention started during the inpatient stay and continued after discharge substantially reduces hospital readmissions [43].

## Conclusions

There is more evidence for the use of  $\beta$ -blockers in the management of heart failure in older people than there is for angiotensin-converting enzyme inhibitors (since angiotensin-converting enzyme inhibitor trials have recruited fewer subjects over the age of 70 [44]).  $\beta$ -blocker treatment in MERIT-HF and CIBIS II reduced mortality by 34% and sudden death by 41% and 44% respectively. This compares favourably with the angiotensin-converting enzyme inhibitor trials, which had a combined reduction in mortality of 24% and no consistent impact on sudden death [45, 46]. Sub-analyses of two trials, MERIT and CIBIS II, have shown mortality reductions in patients aged 70–80 similar to those achieved in younger patients. Evidence is still lacking beyond the age of 80.

$\beta$ -blockers have been used only in patients already stabilized on angiotensin-converting enzyme inhibitors and are not recommended in acute left ventricular failure. Given the compelling evidence, good drug tolerability in trials and the burden of heart failure, it behoves us to develop services to enable older people to benefit maximally from these drugs.

## Key points

- Large-scale, randomized controlled trials have shown that three  $\beta$ -blockers—carvedilol, bisoprolol and metoprolol—significantly reduce mortality from heart failure. Sub-analyses of two of the trials, MERIT and CIBIS II, show mortality reductions in patients aged 70–80 years, similar to those seen in younger patients. Evidence is still lacking beyond the age of 80.
- With the exception of those in COPERNICUS, patients were oedema-free, off intravenous therapy and had been on stable conventional therapy for several weeks before commencement of  $\beta$ -blockers.
- $\beta$ -blockers were started at low doses and increased in stepwise fashion every 2–4 weeks towards the target dose. The drugs were well tolerated, with an overall withdrawal rate of about 15%.
- Early data suggest that nurse-led, multidisciplinary interventions are effective in improving compliance and reducing hospital readmissions.

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