Cardiovascular disorders

Heart failure

Robert McKelvie

Drug and invasive treatments

Beta-blockers

In this section:

Summary

Mortality

Compared with placebo (in people with any severity of heart failure) Beta-blockers are more effective at reducing the risk of death in people with heart failure of any severity who are also receiving triple therapy, and in particular ACE inhibitors (high-quality evidence).

Compared with placebo (in people with severe heart failure) Beta-blockers may be more effective at reducing the risk of death in people with severe heart failure who are also taking ACE inhibitors and diuretics with or without digitalis (low-quality evidence).

Beta-blockers in the elderly compared with non-elderly Beta-blockers seem to be equally effective in the elderly and non-elderly at reducing all-cause mortality (moderate-quality evidence).

Hospitalisation

Compared with placebo (in people with any severity of heart failure) Beta-blockers are more effective at reducing hospital admissions in people with heart failure of any severity who are also receiving triple therapy, and in particular ACE inhibitors (high-quality evidence).

Compared with placebo (in people with severe heart failure) Beta-blockers may be more effective at reducing the combined outcome of death and hospital admissions (very low-quality evidence).

Functional improvement

Compared with placebo (in people with any severity of heart failure) Beta-blockers are more effective at increasing the proportion of people with an improvement in function (New York Heart Association functional classification) by at least one class, and at improving exercise time (moderate-quality evidence).

For GRADE evaluation of interventions for heart failure, see table.

Top

Benefits

We found five systematic reviews (search dates 2000, [27] not reported, [28] not reported, [29] not reported [30] , and 2004 [31]) and three subsequent RCTs [30] [32] [33] of the effects of beta-blockers in heart failure.

In people with any severity of heart failure:

The first systematic review (22 RCTs, 10,315 people with heart failure, most receiving triple therapy, and in particular ACE inhibitors) found that beta-blockers significantly reduced the risk of death and hospital admission compared with placebo (death: 444/5273 [8%] with beta-blockers *v* 624/4862 [13%] with placebo, OR 0.65, 95% CI 0.53 to 0.80; hospital admissions: 540/5244 [10%] with beta-blockers *v* 754/4832 [16%] with placebo, OR 0.64, 95% CI 0.53 to 0.79). [27] This is equivalent to three fewer deaths and four fewer hospital admissions per 100 people treated for 1 year. The results were consistent for selective and non-selective beta-blockers. Sensitivity analysis and funnel plots found that publication bias was unlikely. The second systematic review (28 RCTs, 7637 people) examined the effects of beta-blockers on functional status. [31] Of the people included 95% had NYHA class II or III heart failure and were randomised to receive either beta-blocker (4015 people) or placebo (3622 people). The review found that beta-blockers significantly increased the proportion of people who had improved NYHA class by at least one class (OR 1.80 95% CI 1.33 to 2.43, P less than 0.0001) and significantly improved exercise time (mean difference 44.19 seconds, 95% CI 6.62 to 81.75 seconds, P = 0.021).

In people with severe heart failure:

The second systematic review (4 RCTs, 635 people with class IV heart failure, on ACE and diuretic with or without digitalis) found that beta-blockers significantly reduced the risk of death compared with placebo (56/313 [18%] with beta-blockers *v* 81/322 [25%] with placebo; RR 0.71, 95% CI 0.52 to 0.96). [28] The first two subsequent RCTs compared beta-blockers versus placebo in people with New York Heart Association functional class III or IV heart failure. [32] [33] The first RCT (2289 people with class IV heart failure, who were euvolaemic [defined as the absence of rales and ascites and the presence of no more than minimal peripheral oedema] and who had an ejection fraction of less than 25%, but were not receiving intensive care, iv vasodilators, or positive inotropic drugs) compared carvedilol versus placebo over 10.4 months. [32] It was stopped early because of a significant beneficial effect on survival that exceeded the pre-specified interim monitoring boundaries. It found that beta-blockers significantly reduced mortality compared with placebo (130/1156 [11%] with beta-blockers *v* 190/1133 [17%] with placebo; RR 0.65, 95% CI 0.52 to 0.81) and the combined outcome of death or hospital admission (425/1156 [37%] with beta-blockers *v* 507/1133 [45%] with placebo; RR 0.76, 95% CI 0.67 to 0.87). One subsequent report from this RCT found that, compared with placebo, carvedilol significantly reduced days in hospital for any reason or for heart failure compared with placebo (mean days in hospital for any reason: 6.2 per person with carvedilol *v* 8.5 per person with placebo, P = 0.0005; mean days in hospital for heart failure: 2.9 per person with carvedilol *v* 4.9 per person with placebo, P less than 0.0001). [34] Another report from this RCT examined the short-term risks of initiating carvedilol in severe heart failure. [35] During the first 8 weeks of treatment, it found that, compared with placebo, carvedilol did not significantly reduce mortality and the combined outcome of death or hospitalisation compared with placebo (mortality: HR 0.75, 95% CI 0.41 to 1.35; death or hospitalisation for any reason: HR 0.85, 95% CI 0.67 to 1.07). The second RCT compared bucindolol versus placebo in people with severe heart failure (2708 people with class III or IV heart failure and ejection fraction 35% or less; about 70% of the people were white and 24% were black). [33] The RCT was stopped early because of accumulated evidence from other studies. It found that death was more common with placebo, but the difference did not reach significance (411/1354 [30%] with bucindolol *v* 449/1354 [33%] with placebo; HR 0.90, 95% CI 0.78 to 1.02). The RCT found a significant interaction of treatment effect with race (black *v* non-black people). There was no evidence of benefit in black people (HR 1.17, 95% CI 0.89 to 1.53), although there was a significant effect for non-black people (HR 0.82, 95% CI 0.70 to 0.96). The third systematic review (6 RCTs, 13,370 people) examined the magnitude of benefit of beta-blockers in people not taking ACE inhibitors or angiotensin II receptor blockers (ARBs). [29] It found that the reduction in all-cause mortality in people taking beta-blockers without ACE inhibitors or ARBs versus placebo was similar to that in the group taking beta-blockers plus ACE inhibitors or ARBs versus placebo (RR 0.73, 95% CI 0.53 to 1.02 without ACE inhibitors or ARBs *v* RR 0.76, 95% CI 0.71 to 0.83 with ACE inhibitors or ARBs). The review also found that ACE inhibitors (pre-beta-blocker) significantly reduced all-cause mortality versus placebo (RR 0.89, 95% CI 0.80 to 0.99) in studies of less than 90 days' duration. The impact of beta-blocker therapy on death or heart failure hospitalisation in the absence or presence of ACE inhibitors versus placebo was examined (3 RCTs, 8988 people, RR 0.81, 95% CI, 0.16 to 1.08 without ACE inhibitors or ARBs compared with RR 0.78, 95% CI, 0.74 to 0.83 with ACE inhibitors or

ARBs). When ACE inhibitors were analysed in the same way (pre-beta-blocker), an RR of 0.85 (95% CI 0.78 to 0.93) versus placebo was observed in studies of less than 90 days' duration. These data suggest that the magnitude of the prognostic benefit conferred by beta-blockers in the absence of ACE inhibitors or ARBs appears to be similar to that of ACE inhibitors. Therefore, the data suggest that either ACE inhibitors or beta-blockers could be used as first-line therapy in systolic heart failure. [29] The third subsequent RCT (1010 people not receiving ACE inhibitors, beta-blockers, or ARBs) randomised people to receive either bisoprolol (10 mg daily, 505 people) or enalapril (10 mg twice daily, 505 people) for 6 months, followed by their combination for 6–24 months. [36] The primary end point of all-cause mortality or hospitalisation was reached in 178 (35%) people receiving bisoprolol first and in 186 (37%) people receiving enalapril first (HR 0.94, 95% CI 0.77 to 1.16). In the intention to treat analysis, bisoprolol was found to be non-inferior compared with enalapril. These data suggest that bisoprolol may be as safe and efficacious as enalapril for treating heart failure. [36]

In elderly people:

The fourth systematic review (5 RCTs, 17,346 people) examined whether beta-blockers are as effective in the elderly as they are in the non-elderly for chronic heart failure. [30] The cut-off points for the elderly age-ranges varied across trials (59–71 years). The review found that the use of beta-blocker therapy significantly reduced all-cause mortality for the non-elderly (RR 0.66, 95% CI 0.52 to 0.85; P = 0.001) and the elderly (RR 0.76, 95% CI 0.64 to 0.90; P = 0.002), without a statistically significant difference in mortality reduction between the two groups (P = 0.38). [30]

Top

Harms

Two systematic reviews and one subsequent RCT gave no information on adverse effects. [29] [30] [36] One systematic review (search date 2002, 9 RCTs, 14,594 people followed up for 6–24 months) assessed harms of beta-blockers in people with heart failure. [37] It found that beta-blockers reduced the risk of withdrawal from treatment, death, and worsening heart failure compared with placebo (withdrawal: 16% with beta-blockers *v* 18% with placebo, RR 0.89, 95% CI 0.81 to 0.98; death: 13% with beta-blockers *v* 17% with placebo, RR 0.73, 95% CI 0.62 to 0.85; worsening heart failure: 4 RCTs, RR 0.83, 95% CI 0.71 to 0.98). It found that beta-blockers significantly increased dizziness and bradycardia, but there was no significant difference between treatments for hypotension and fatigue compared with placebo (dizziness: 4 RCTs, RR 1.37, 95% CI 1.09 to 1.71; bradycardia: 7 RCTs, RR 3.62, 95% CI 2.48 to 5.28; hypotension: 7 RCTs, RR 1.41, 95% CI 0.96 to 2.06; fatigue: 3 RCTs, RR 1.04, 95% CI 0.97 to 1.11).

Top

Comment

Fears that beta-blockers may cause excessive problems with worsening heart failure, bradyarrhythmia, or hypotension have not been confirmed. Good evidence was found for beta-blockers in people with moderate symptoms (New York Heart Association functional class II or III) receiving standard treatment, including ACE inhibitors. The value of beta-blockers is uncertain in heart failure with preserved ejection fraction and in asymptomatic left ventricular systolic dysfunction. One RCT (1959 people) found that carvedilol reduced all-cause mortality compared with placebo (AR for death: 12% with carvedilol *v* 15% with placebo; HR 0.77, 95% CI 0.60 to 0.98) in people with acute myocardial infarction and left ventricular ejection fraction 40% or less. [38]

Effects of different beta-blockers:

The RCTs of beta-blockers have consistently found a mortality benefit, but it is not clear whether this is a class effect. One small RCT (150 people) comparing metoprolol versus carvedilol found some differences in surrogate outcomes, but both drugs produced similar improvements in symptoms, submaximal exercise tolerance, and quality of life. [39] Another RCT (3029 people) compared carvedilol versus metoprolol tartrate in people with heart failure. [40] It found that carvedilol significantly reduced all-cause mortality compared with metoprolol (512/1511 [34%] with carvedilol *v* 600/1518 [40%] with metoprolol; HR 0.83, 95% CI 0.74 to 0.93). It found no significant difference between groups for the composite outcome of mortality or all-cause admission (P = 0.122). The results of this RCT suggest that carvedilol extends survival compared with metoprolol. However, potential limitations to this RCT were that the target dose of metoprolol was lower than that usually suggested, and that the formulation of metoprolol used was not the long-acting formulation used in a previous RCT, [33] which had shown significant clinical benefit. The results for non-black people were consistent between bucindolol and carvedilol.

Effects in different populations:

The lack of observed benefit for black people in one RCT [33] raises the possibility that there may be race specific responses to pharmacological treatment for cardiovascular disease. There may also be different responses in people with diabetes mellitus. A meta-analysis (6 RCTs, 13,129 people) examined whether beta-blockers in people with heart failure are as efficacious in those with as without diabetes mellitus. [41] It found that overall mortality was significantly increased in people with diabetes mellitus compared with people without diabetes mellitus, regardless of treatment (RR 1.25, 95% CI 1.15 to 1.36). Carvedilol has also been assessed in people with diabetes in a meta-analysis because it is believed that carvedilol has unique characteristics compared with other beta-blockers. [42] In this meta-analysis, 7 RCTs were examined (5757 people, 25% with diabetes mellitus) to determine if the effects of carvedilol were similar in people with and without diabetes mellitus. There was no significant difference in mortality or the number needed to treat (NNT) to prevent 1 death for one year for people with or without diabetes (mortality in people with diabetes: carvedilol *v* placebo: RRR 28%, 95% CI 3 to 46%, P = 0.03; people without diabetes: RRR 37%, 95% CI 22 to 48%, P less than 0.001; difference between 2 groups reported as not significant, P value not reported; NNT 25,

95% CI 14 to 118 for people with diabetes mellitus *v* NNT 23, 95% CI 17 to 37 for people without diabetes mellitus). Although beta-blockers significantly reduced mortality compared with placebo in people with diabetes mellitus (RR 0.84, 95% CI 0.73 to 0.96), the magnitude of benefit was significantly lower than that in people who did not have diabetes mellitus (P = 0.023).One RCT (2128 elderly people with heart failure, mean age 76 years, mean left ventricular ejection fraction 36%, 35% of people had ejection fraction of more than 35%) examined the effects of nebivolol in the elderly. [43] It found that nebivolol significantly reduced the composite end-point of all-cause mortality or cardiovascular hospital admission compared with placebo (31.1% with nebivolol *v* 35.3% with placebo; HR 0.86, 95% CI 0.74 to 0.99). It found no significant difference between treatments in all-cause mortality (16% with nebivolol *v* 18% with placebo; HR 0.88, 95% CI 0.71 to 1.08). The absence of a significant effect of nebivolol on death may have been because of the inclusion of many people with a left ventricular ejection fraction above 35%.

References

27. Brophy JM, Joseph L, Rouleau JL. Beta-blockers in congestive heart failure: a Bayesian meta-analysis. *Ann Intern Med* 2001;134:550–560. Search date 2000; primary sources Medline, Cochrane Library, Web of Science, and hand searches of reference lists from relevant articles. [PubMed]

28. Whorlow SL, Krum H. Meta-analysis of effect of beta-blocker therapy on mortality in patients with New York Heart Association class IV chronic congestive heart failure. *Am J Cardiol* 2000;86:886–889. Search date not reported; primary sources Medline and hand searches of reference lists from relevant reviews. [PubMed]

29. Krum H, Haas SJ, Eichhorn E, et al. Prognostic benefit of beta-blockers in patients not receiving ACE-inhibitors. *Eur Heart J* 2005;26:2154–2158. [PubMed]

30. Dulin BR, Haas SJ, Abraham WT, et al. Do elderly systolic heart failure patients benefit from beta blockers to the same extent as the non-elderly? Meta-analysis ofmore than 12,000 patients in large-scale clinical trials. *Am J Cardiol* 2005;95:896–898. [PubMed]

31. Abdulla J, Kober L, Christensen E, et al. Effect of beta-blocker therapy on functional status in patients with heart failure - A meta-analysis. *European Journal of Heart Failure* 2006;8:522-531

32. Packer M, Coats A, Fowler MB. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;344:1651–1658. [PubMed]

33. The Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med* 2001;344:1659–1667. [PubMed]

34. Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation* 2002;106:2194–2199. [PubMed]

35. Krum H, Roecker EB, Mohacsi P, et al. Effects of initiating carvedilol in patients with severe chronic heart failure: results from the COPERNICUS Study. *JAMA* 2003;289:712–718. [PubMed]

36. Willenheimer R, van Veldhuisen DJ, Silke B, et al. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: results of the Randomized Cardiac Insufficiency Bisoprolol study (CIBIS) III. *Circulation* 2005;112:2426–2435. [PubMed]

37. Ko DT, Hebert PR, Coffey CS, et al. Adverse effects of beta-blocker therapy for patients with heart failure. A quantitative overview of randomised trials. *Arch Intern Med* 2004;164:1389–1394. Search date 2002; primary sources Medline, reference lists of included studies and reviews. [PubMed]

38. The CAPRICORN Investigators. Effect of carvedilol on outcome after myocardial infarction in patients with left ventricular dysfunction: the CAPRICORN randomized trial. *Lancet* 2001;357:1385–1390. [PubMed]

39. Metra M, Giubbini R, Nodari S, et al. Differential effects of beta-blockers in patients with heart failure: a prospective, randomized, double-blind comparison of the long-term effects of metoprolol versus carvedilol. *Circulation* 2000;102:546–551. [PubMed]

40. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet* 2003;362:7–13. [PubMed]

41. Haas SJ, Vos T, Gilbert RE, et al. Are beta-blockers as efficacious in patients with diabetes mellitus as in patients without diabetes mellitus who have chronic heart failure? A meta-analysis of large-scale clinical trials. *Am Heart J* 2003;146:848–853. [PubMed]

42. Bell DSH, Lukas MA, Holdbrook FK, et al. The effect of carvedilol on mortality risk in heart failure patients with diabetes: Results of a meta-analysis. *Current Medical Research & Opinion* 2006;22:287-296

43. Flather MD, Shibata MC, Coats AJS, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005;26:215–225. [PubMed]