Robert McKelvie

Drug and invasive treatments

ACE inhibitors for treating heart failure

In this section:

Summary

Mortality

Compared with placebo ACE inhibitors are more effective at reducing mortality (high-quality evidence).

Different doses compared with each other Low-dose and high-dose lisinopril seem equally effective at reducing mortality (moderate-quality evidence).

Compared with Angiotensin II receptor blockers ACE inhibitors and Angiotensin II receptor blockers seem equally effective at reducing all-cause mortality at 4 weeks to 2.7 years (moderate-quality evidence).

ACE inhibitors

alone compared with Angiotensin II receptor blockers plus ACE inhibitors Adding Angiotensin II receptor blockers to ACE inhibitors may be no more effective at reducing mortality than ACE inhibitors alone (low-quality evidence).

Hospitalisation

Compared with placebo ACE inhibitors are more effective at reducing hospital admissions for heart failure (high-quality evidence).

Different doses compared with each other Low-dose lisinopril is less effective than high-dose lisinopril at reducing admissions for heart failure (moderate-quality evidence).

Compared with Angiotensin II receptor blockers ACE inhibitors and Angiotensin II receptor blockers seem equally effective at 4 weeks to 2.7 years at reducing hospitalisations for heart failure (moderate-quality evidence).

ACE inhibitors

alone compared with Angiotensin II receptor blockers plus ACE inhibitors Adding Angiotensin II receptor blockers to ACE inhibitors is more effective at reducing hospitalisations for heart failure than ACE inhibitors alone (moderate-quality evidence).

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

Top

Benefits

Angiotensin converting enzyme (ACE) inhibitors versus placebo:

We found two systematic reviews (search dates 1994 [20] and not reported [21]) of ACE inhibitors versus placebo in heart failure. The first review (32 RCTs, duration 3–42 months, 7105 people, New York Heart Association functional class III or IV) found that ACE inhibitors significantly reduced mortality compared with placebo (611/3870 [16%] with ACE inhibitors *v* 709/3235 [22%] with placebo; ARR 6%, 95% CI 4% to 8%; OR 0.77, 95% CI 0.67 to 0.88). [20] Relative reductions in mortality were similar in different subgroups (stratified by age, sex, cause of heart failure, and New York Heart Association functional class). The second review (5 RCTs, 12,763 people with left ventricular dysfunction or heart failure of mean duration 35 months) analysed long-term results from large RCTs comparing ACE inhibitors versus placebo. [21] Three RCTs examined the effects of ACE inhibitors in people for 1 year after myocardial infarction. In these three postinfarction trials (5966 people), ACE inhibitors compared with placebo significantly reduced mortality (702/2995 [23%] with ACE inhibitors *v* 866/2971 [29%] with placebo; OR 0.74, 95% CI 0.66 to 0.83), re-admission for heart failure (355/2995 [12%] with ACE inhibitors *v* 460/2971 [16%] with placebo; OR 0.73, 95% CI 0.63 to 0.85), and re-infarction (324/2995 [11%] with ACE inhibitors *v* 391/2971 [13%] with placebo; OR 0.80, 95% CI 0.69 to 0.94). For all five trials, ACE inhibitors compared with placebo significantly reduced mortality (1467/6391 [23%] with ACE inhibitors *v* 1710/6372 [27%] with placebo; OR 0.80, 95% CI 0.74 to 0.87), re-infarction (571/6391 [9%] with ACE inhibitors *v* 703/6372 [11%] with placebo; OR 0.79, 95% CI 0.70 to 0.89), and re-admission for heart failure (876/6391 [14%] with ACE inhibitors *v* 1202/6372 [19%] with placebo; OR 0.67, 95% CI 0.61 to 0.74). The relative benefits began soon after the start of treatment, persisted in the long term, and were independent of age, sex, and baseline use of diuretics, aspirin, and beta-blockers. Although there was a trend toward greater relative reduction in mortality or re-admission for heart failure in people with lower ejection fraction, benefit was apparent over the range examined.

Dose:

We found one large RCT (3164 people with New York Heart Association functional class II–IV heart failure), which compared low-dose lisinopril (2.5 or 5.0 mg/day) versus high-dose lisinopril (32.5 or 35.0 mg/day). [22] It found no significant difference in mortality (717/1596 [45%] with low dose *v* 666/1568 [43%] with high dose; ARR 2.4%, CI not reported; HR 0.92, 95% CI 0.80 to 1.03; P = 0.128), but found that high-dose lisinopril reduced the combined outcome of death or hospital admission for any reason (events: 1338/1596 [84%] with low dose *v* 1250/1568 [80%] with high dose; ARR 4.1%, CI not reported; HR 0.88, 95% CI 0.82 to 0.96) and reduced admissions for heart failure (admissions: 1576/1596 [99%] with low dose *v* 1199/1568 [77%] with high dose; ARR 22.2%, CI not reported; P = 0.002).

Comparison of different ACE inhibitors:

The first systematic review found similar benefits with different ACE inhibitors. [20]

ACE inhibitors versus Angiotensin II inhibitors:

See benefits of Angiotensin II inhibitors.

ACE inhibitors alone versus ACE inhibitors plus Angiotensin II receptor blockers:

See benefits of Angiotensin II inhibitors.

Top

Harms

The main adverse effects in large RCTs were cough, hypotension, hyperkalaemia, and renal dysfunction.We found one systematic review (search date 1999), which specifically examined the adverse effects of ACE inhibitors in people with heart failure. [23] It found that ACE inhibitors significantly increased withdrawal because of adverse effects compared with control (placebo or non-ACE inhibitor treatments) after about 2 years (22 RCTs, 9668 people; AR 13.8% with ACE inhibitor *v* 9.4% with

control; RR 1.54, 95% CI 1.30 to 1.83). ACE inhibitors significantly increased cough, hypotension, renal dysfunction, dizziness, and impotence compared with control treatments (cough: RR 3.19, 95% CI 2.22 to 4.57; hypotension: RR 1.95, 95% CI 1.39 to 2.74; renal dysfunction: RR 1.84, 95% CI 1.20 to 2.81; dizziness: RR 1.60, 95% CI 1.15 to 2.23; impotence: RR 6.46, 95% CI 1.14 to 36.58).

Angiotensin converting enzyme (ACE) inhibitors versus placebo:

Compared with placebo, ACE inhibitors increased cough (37% with ACE inhibitor *v* 31% with placebo; ARI 7%, 95% CI 3% to 11%; RR 1.23, 95% CI 1.11 to 1.35), dizziness or fainting (57% with ACE inhibitor *v* 50% with placebo; ARI 7%, 95% CI 3% to 11%; RR 1.14, 95% CI 1.06 to 1.21), increased creatinine concentrations above 177 mumol/L (11% with ACE inhibitor *v* 8% with placebo; ARI 3.0%, 95% CI 0.6% to 6.0%; RR 1.38, 95% CI 1.09 to 1.67), and increased potassium concentrations above 5.5 mmol/L (AR 6% with ACE inhibitor *v* 3% with placebo; ARI 4%, 95% CI 2% to 7%; RR 2.56, 95% CI 1.92 to 3.20). [24] The risk of angio-oedema was similar with ACE inhibitors and placebo (3.8% with enalapril *v* 4.1% with placebo; ARI + 0.3%, 95% CI – 1.4% to + 1.5%). [24]

Dose:

The trial comparing low- versus high-dose lisinopril found that adverse effects were more common with high dose (dizziness: 12% with low dose *v* 19% with high dose; hypotension: 7% with low dose *v* 11% with high dose; worsening renal function: 7% with low dose *v* 10% with high dose; significant change in serum potassium concentration: 7% with low dose *v* 7% with high dose; P values not reported), although there was no difference in withdrawal rates between groups (18% discontinued with low dose *v* 17% with high dose). [22] The trial found that cough was less commonly experienced with high-dose than low-dose lisinopril (cough: 13% with low dose *v* 11% with high dose).

ACE inhibitors versus Angiotensin II inhibitors:

See harms of Angiotensin II inhibitors.

ACE inhibitors alone versus ACE inhibitors plus Angiotensin II receptor blockers:

See harms of Angiotensin II inhibitors.

Top

Comment

The relative benefits of ACE inhibitors were similar in different subgroups of people with heart failure. Most RCTs evaluated left ventricular function by assessing left ventricular ejection fraction, but some studies defined heart failure clinically, without measurement of left ventricular function in people at high risk of developing heart failure (soon after myocardial infarction). It is unclear whether there are additional benefits from adding an ACE inhibitor to antiplatelet treatment in people with heart failure (see antiplatelet agents).

References

20. Garg R, Yusuf S, for the Collaborative Group on ACE Inhibitor Trials. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. *JAMA* 1995;273:1450–1456. Search date 1994; primary sources Medline and correspondence with investigators and pharmaceutical companies. [PubMed]

21. Flather M, Yusuf S, Kober L, et al, for the ACE-Inhibitor Myocardial Infarction Collaborative Group. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. *Lancet* 2000;355:1575–1581. Search date not reported; primary sources Medline, Ovid, hand searches of reference lists, and personal contact with researchers, colleagues, and principal investigators of the trials identified. [PubMed]

22. Packer M, Poole-Wilson PA, Armstrong PW, et al, on behalf of the ATLAS Study Group. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. *Circulation* 1999;100:2312–2318. [PubMed]

23. Agusti A, Bonet S, Arnau JM, et al. Adverse effects of ACE inhibitors in patients with chronic heart failure and/or ventricular dysfunction: meta-analysis of randomized clinical trials. *Drug Saf* 2003;26:895–908. Search date 1999; primary sources Medline, Embase, references lists, relevant reviews, contact with authors of reports, experts in the field, and pharmaceutical companies. [PubMed]

24. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293–302. [PubMed]