Diabetes: treating hypertension

Sandeep Vijan

Treatments

Angiotensin-converting enzyme inhibitors

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Summary

One systematic review found that angiotensin-converting enzyme (ACE) inhibitors reduced microalbuminuria (an early sign of renal dysfunction) compared with placebo and calcium channel blockers. One RCT found that ramipril (an ACE inhibitor) reduced cardiovascular events and nephropathy compared with placebo. One RCT found that trandolapril reduced microalbuminuria (an early sign of renal dysfunction) compared with placebo. One RCT found that chlorthalidone (a diuretic) was at least as effective as lisinopril (an ACE inhibitor) at reducing cardiovascular events. The systematic review found no significant difference in the rate of onset of microalbuminuria between angiotensin-converting enzyme inhibitors and beta-blockers. One RCT found no significant difference in cardiovascular events, microvascular events, or diabetes-related death between atenolol (a beta-blocker) and captopril (an ACE inhibitor), although atenolol led to greater weight gain and a greater need for glucose-lowering therapy. Two RCTs found that ACE inhibitors (fosinopril and enalapril) reduced cardiovascular events compared with calcium channel blockers (amlodipine and nisoldipine). Another RCT found that trandolapril (an ACE inhibitor) alone reduced onset of microalbuminuria compared with verapamil (a calcium channel blocker) alone, and found a similar incidence of microalbuminuria with trandolapril alone and trandolapril plus verapamil. We found no RCTs comparing ACE inhibitors versus alpha-blockers, or angiotensin II receptor antagonists.

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Benefits

ACE inhibitors versus placebo:

We found one systematic review, [13] one additional RCT, [14] and one subsequent RCT. [15] The systematic review (search date 2003) found that ACE inhibitors significantly reduced the onset of microalbuminuria (an early sign of renal dysfunction) compared with placebo (4 RCTs, 3284 people; RR 0.52, 95% CI 0.31 to 0.88; absolute numbers not reported). [13] The additional RCT (3577 people with type 1 or 2 diabetes [98% type 2]; mean age 65.3 years; mean blood pressure 142/80 mm Hg), found that ramipril 10 mg daily significantly reduced combined cardiovascular outcomes (RR 0.75, 95% CI 0.64 to 0.88) and development of diabetic nephropathy (RR 0.76, 95% CI 0.60 to 0.97) compared with placebo over 4.5 years. [14] The subsequent RCT compared four treatments over 3 years: trandolapril 2 mg daily, verapamil 240 mg daily, trandolapril 2 mg daily plus verapamil 180 mg daily, and placebo. [15] Additional antihypertensive drugs were allowed to achieve target blood pressure. It found that trandolapril significantly reduced microalbuminuria compared with placebo (4-arm RCT, 1209 people with type 2 diabetes; mean age 62 years; mean blood pressure 151/87 mm Hg; AR of microalbuminuria: 18/301 [6%] with trandolapril *v* 30/300 [10%] with placebo; acceleration factor 0.47, 95% CI 0.26 to 0.83).

ACE inhibitors versus beta-blockers:

See benefits of beta-blockers versus angiotensin-converting enzyme inhibitors.

ACE inhibitors versus alpha-blockers:

We found no RCTs.

ACE inhibitors versus diuretics:

See benefits of diuretics versus angiotensin-converting enzyme inhibitors.

ACE inhibitors versus calcium channel blockers:

The systematic review found that ACE inhibitors significantly reduced the onset of microalbuminuria compared with calcium channel blockers (4 RCTs, 1210 people; RR 0.58, 95% CI 0.40 to 0.84; absolute numbers not reported). [13] We found two additional RCTs that were published within the search date of the review [16] [17] and one subsequent RCT (see comment below). [15] The first additional RCT (380 people with type 2 diabetes; mean age 63 years; mean blood pressure 170/95 mm Hg) found that fosinopril significantly reduced cardiovascular events at a mean of 2.5 years' follow-up compared with amlodipine (HR 0.49, 95% CI 0.26 to 0.95). [16] The second additonal RCT (470 people with type 2 diabetes; mean age 57.5 years; 68% male; mean blood pressure 155/98 mm Hg) found that enalapril significantly reduced the risk of myocardial infarction after 5 years compared with nisoldipine (25/235 [11%] with nisoldipine *v*

5/235 [2%] with enalapril; ARI 9%, 95% CI 4% to 13%; RR 5.5, 95% CI 2.1 to 14.6). [17] However, it found no significant difference in stroke, congestive heart failure, or cardiovascular mortality (stroke: 11/235 [5%] with nisoldipine *v* 7/235 [3%] with enalapril; RR 1.6, 95% CI 0.6 to 4.2; congestive heart failure; 6/235 [3%] with nisoldipine *v* 5/235 [2%] with enalapril; RR 1.2, 95% CI 0.4 to 4.0; cardiovascular mortality: 10/235 [4%] with nisoldipine *v* 5/235 [2%] with enalapril; RR 2.0, 95% CI 0.7 to 6.1). The subsequent RCT compared four treatments over 3 years trandolapril 2 mg daily, verapamil 240 mg daily, trandolapril 2 mg daily plus verapamil 180 mg daily, and placebo. [15] Additional antihypertensive drugs were allowed to achieve target blood pressure. The RCT found that trandolapril significantly reduced microalbuminuria compared with verapamil (AR for microalbuminuria: 18/301 [6%] with trandolapril *v* 36/303 [12%] with verapamil; acceleration factor 0.53, 95% CI 0.29 to 0.96).

ACE inhibitors versus angiotensin II receptor antagonists:

We found no RCTs.

ACE inhibitors alone versus combinations including ACE inhibitors:

We found one RCT which compared four treatments over 3 years trandolapril 2 mg daily, verapamil 240 mg daily, trandolapril 2 mg daily plus verapamil 180 mg daily, and placebo. [15] Additional antihypertensive drugs were allowed to achieve target blood pressure. The RCT found a similar incidence of microalbuminuria with trandolapril alone and trandolapril plus verapamil (development of microalbuminuria: 18/301 [6.0%] with trandolapril *v* 17/300 [5.7%] with trandolapril plus verapamil; significance assessment not performed).

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Harms

ACE inhibitors versus placebo:

The systematic review gave no information on adverse effects. [13] The first RCT found that ACE inhibitors increased the proportion of people with cough (7% with ramipril *v* 2% with placebo) and angio-oedema (0.3% with ramipril *v* 0.1% with placebo) compared with placebo. [14] The second RCT found a similar rate of non-fatal serious adverse events with trandolapril and placebo (27% with trandolapril *v* 23% with placebo; significance assessment not performed). [15]

ACE inhibitors versus beta-blockers:

See harms of beta-blockers versus angiotensin-converting enzyme inhibitors.

ACE inhibitors versus diuretics:

See harms of diuretics versus angiotensin-converting enzyme inhibitors.

ACE inhibitors versus calcium channel blockers:

The systematic review gave no information on adverse effects. [13] The first RCT gave no information on adverse effects. [16] The second RCT found that enalapril significantly reduced the proportion of people experiencing headaches compared with nisoldipine (10/235 [4.3%] with nisoldipine *v* 1/235 [0.4%] with enalapril; P less than 0.05). [17] However, enalapril significantly increased fatigue (0/235 [0%] with nisoldipine *v* 7/235 [3%] with enalapril; P less than 0.05). The additional RCT found a similar rate of non-fatal serious adverse events with trandolapril and verapamil (AR of non-fatal serious adverse event: 27% with trandolapril *v* 22% with verapamil; significance assessment not performed). [15] One person (0.3%) taking verapamil developed atrioventricular block.

ACE inhibitors versus angiotensin II receptor antagonists:

We found no RCTs.

ACE inhibitors alone versus combinations including ACE inhibitors:

The RCT found no significant differences in non-fatal serious adverse effects between trandolapril and trandolapril plus verapamil (AR of non-fatal serious adverse effect: 27% with trandolapril *v* 22% with trandolapril plus verapamil; significance assessment not performed). [15] One person (0.3%) taking trandolapril plus verapamil developed sinoatrial block with junctional rhythm.

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Comment

The four-arm RCT reported in this option is also reported in the calcium channel blocker option. [15] We found one RCT that compared three treatments in people with hypertension: an ACE inhibitor (lisinopril), a diuretic (chlorthalidone), and a calcium channel blocker (amlodipine). [18] It did not provide a comparison of lisinopril versus amlodipine in the subgroup of people with diabetes. [18]

Clinical guide:

ACE inhibitors are effective in reducing cardiovascular and renal risk in people with diabetes, and are a reasonable first-line treatment option.

References

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