Diabetic nephropathy

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Type 2 diabetes and late nephropathy

Angiotensin II receptor antagonists

In this section:

Summary

Mortality

Compared with placebo Angiotensin II receptor antagonists may be no more effective than placebo at decreasing all-cause mortality compared with placebo in people with mainly late-stage nephropathy and type 2 diabetes (low-quality evidence).

Compared with ACE inhibitors We don't know how angiotensin II receptor antagonists and ACE inhibitors compare for reducing mortality (moderate-quality evidence).

End stage renal failure

Compared with placebo Angiotensin II receptor antagonists may reduce the risk of end stage renal disease compared with placebo in people with type 2 diabetes with late stage nephropathy (very low-quality evidence).

Note

We found no clinically important results about the effects of combined angiotensin II receptor antagonists plus ACE inhibitors in people with type 2 diabetes and late nephropathy.

For GRADE evaluation of interventions for diabetic nephropathy, see table.

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Benefits

Angiotensin II receptor antagonists versus placebo:

We found one systematic review (search date 2005, 5 RCTs, 3409 people), which compared angiotensin II receptor antagonists with placebo for end stage renal disease and all cause mortality. [36] It combined RCTs of early and late nephropathy, but most people had late nephropathy. The review found no significant difference in all cause mortality with angiotensin II receptor antagonists compared with placebo (248/1813 [14%] with angiotensin II receptor antagonists *v* 249/1596 [16%] with placebo; RR 0.99, 95% CI 0.85 to 1.17). The review also found that angiotensin II receptor antagonists significantly reduced end stage renal disease compared with placebo (3 RCTs, 3251 people; 229/1719 [13.3%] with angiotensin II receptor antagonists *v* 195/1532 [12.7%] with placebo; RR 0.78, 95% CI 0.67 to 0.91). Most people included in the review were from two RCTs. The first RCT found that losartan significantly reduced progression to end stage renal disease over 3.4 years compared with placebo (1513 people with type 2 diabetes and urine albumin/creatinine ratio ≥ 300 mg/g [34 mg/mmol] and serum creatinine levels of 1.3–3.0 mg/dL; progression to end stage renal disease: 147/751 [20%] with losartan *v* 194/762 [26%] with placebo; RR 0.72, 95% CI 0.58 to 0.89; ARR 2.3/100 person years). It found no significant difference in fatal or non-fatal cardiovascular events or death from any cause (fatal or non-fatal cardiovascular events: 247/751 [33%] with losartan *v* 268/762 [35%] with placebo; RR 0.94, 95% CI 0.81 to 1.08; death from any cause: 158/751 [21%] with losartan *v* 155/762 [20%] with placebo; RR 1.03, 95% CI 0.85 to 1.26). Both losartan and placebo were taken in addition to conventional antihypertensive treatment (calcium channel blockers, diuretics, alpha-blockers, and beta-blockers). [37] The second RCT found no significant difference between irbesartan and placebo in progression to end stage renal disease, or death from any cause over 2.6 years, in people with type 2 diabetes and late nephropathy (1715 people with type 2 diabetes, hypertension, proteinuria > 900 mg [median 2.9 g/day] and serum creatinine 1.0–3.0 mg/dL; progression to end stage renal disease: 82/579 [14%] with irbesartan *v* 101/569 [18%] with placebo; RR 0.77, 95% CI 0.57 to 1.03; P = 0.07; death from any cause: RR 0.92, 95% CI 0.69 to 1.23). [38] A second publication of this RCT reported that irbesartan significantly reduced the incidence of congestive heart failure compared with placebo (80/579 [14%] with irbesartan *v* 113/569 [20%] with placebo; RR 0.72, 95% CI 0.52 to 1.00; P = 0.048). It found no significant difference for a composite cardiovascular outcome, cardiovascular death, myocardial infarction, cerebrovascular accident, or cardiac revascularisation (composite cardiovascular outcome: 259/579 [45%] with irbesartan *v* 284/569 [50%] with placebo; RR 0.90, 95% CI 0.74 to 1.10; P > 0.2; cardiovascular death: 52/579 [9%] with irbesartan *v* 46/569 [8%] with placebo; RR 1.08, 95% CI 0.72 to 1.60; P > 0.2; myocardial infarction: 48/579 [8%] with irbesartan *v* 51/569 [9%] with placebo; RR 0.90, 95% CI 0.60 to 1.33; P > 0.2; cerebrovascular accident: 30/579 [5%] with irbesartan *v* 28/569 [5%] with placebo; RR 1.01, 95% CI 0.61 to 1.67; P > 0.2; cardiac revascularisation: 31/579 [5%] with irbesartan *v* 39/569 [7%] with placebo; RR 0.80, 95% CI 0.49 to 1.30; P > 0.2). [39]

Angiotensin II receptor antagonists versus ACE inhibitors:

We found one systematic review (search date 2005, 3 RCTs, 307 people), which found no significant difference in all cause mortality with angiotensin II receptor antagonists compared with ACE inhibitors (6/157 [3.8%] with angiotensin II receptor antagonists *v* 6/150 [4.0%] with ACE inhibitors; RR 0.92, 95% CI 0.31 to 2.78). [36] Given this wide confidence interval, this review cannot exclude large differences between the two drug classes.

Angiotensin II receptor antagonists plus ACE inhibitors:

We found no systematic review or RCTs.

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Harms

Angiotensin II receptor antagonists versus placebo:

The review reported that there was a significant increase in the risk of hyperkalaemia with angiotensin II receptor antagonists compared with placebo (2 RCTs, 2287 people; 22/1153 [2%] with angiotensin II receptor antagonists *v* 4/1134 [0.4%] with placebo; RR 5.41, 95% CI 1.87 to 15.65). [36] The first RCT included in the review found that, overall, a lower proportion of people discontinued medication with losartan compared with placebo (1513 people; 47% with losartan *v* 54% with placebo; absolute numbers and significance data not reported). It found that a higher proportion of people discontinued treatment because of hyperkalaemia with losartan compared with placebo (1.1% with losartan *v* 0.5% with placebo; absolute numbers and significance data not reported). [37] Similarly, the second RCT included in the review found that a significantly higher proportion of people discontinued treatment because of hyperkalaemia with irbesartan compared with placebo (1715 people; hyperkalaemia: 11/579 [1.9%] with irbesartan *v* 2/569 [0.4%] with placebo; P = 0.01). [38]

Angiotensin II receptor antagonists versus ACE inhibitors:

The review did not report on harms.

Angiotensin II receptor antagonists plus ACE inhibitors:

We found no RCTs.

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Comment

In both RCTs (RENAAL [Reduction in Endpoints with the Angiotensin II Antagonist Losartan] and IDNT [Irbesartan Diabetic Nephropathy Trial]), the primary outcome was a composite end point of the doubling of serum creatinine, end stage renal disease, or death. [37] [38] In each RCT, the angiotensin II receptor antagonist (losartan or irbesartan) significantly reduced the incidence of the primary outcome compared with placebo. In this review, we have focused only on the clinical outcomes of end stage renal disease, cardiovascular events, and death.

References

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