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COCHRANE COMMENTARIES

Edited by Angela Webster (angela.webster@sydney.edu.au)
Written by Min Jun (mjun@georgeinstitute.org.au)

Antioxidants for chronic kidney disease

What is this review about?

This review summarized the randomized trials using antioxidant therapy (vitamins A, C, E, β-carotene, N-acetyl cysteine) in patients with chronic kidney disease (CKD) stages 3–5, dialysis patients and transplantation patients. We focused on the benefits and harms of antioxidant therapy on cardiovascular outcomes and mortality in addition to renal outcomes including serum creatinine, estimated glomerular filtration rate (eGFR), and end-stage kidney disease (ESKD).

What are the key findings?

When compared with placebo, antioxidant therapy had no overall effect on the risk of cardiovascular death (Fig. 1) (3 trials, 1323 participants; relative risk (RR) 0.95, 95% confidence interval (CI): 0.70–1.27), major cardiovascular disease (4 trials, 1550 participants; RR 0.78, 95% CI: 0.52–1.18), all-cause death (5 trials, 1727 participants; RR 0.93, 95% CI: 0.76–1.14), coronary events (4 trials, 1550 participants; RR 0.72, 95% CI: 0.42–1.23), cerebrovascular events (3 trials, 1323 participants; RR 0.91, 95% CI: 0.63–1.32), or peripheral vascular disease (2 trials, 330 participants; RR 0.54, 95% CI: 0.26–1.12). Subgroup analyses, however, showed significant heterogeneity by CKD stage for cardiovascular disease ($I^2 = 67.1\%$, $P = 0.03$) with no effect in the CKD population (2 trials, 1220 participants; RR 1.06; 95% CI: 0.84–1.32) and a beneficial effect in dialysis patients (2 trials, 330 participants; RR 0.57; 95% CI: 0.41–0.80) (Fig. 2). Similar heterogeneity was identified for coronary events ($I^2 = 48\%$, $P = 0.12$). For those with CKD stages 3 and 4 and kidney transplant recipients, antioxidant therapy significantly reduced the risk of ESKD (2 trials, 404 participants; RR 0.50, 95% CI: 0.25–1.00), reduced serum creatinine levels (5 trials, 234 participants; mean difference (MD): 1.10 mg/dL, 95% CI: 0.39–1.81), and improved creatinine clearance (4 trials, 195 participants; MD 14.53 mL/min; 95% CI: 1.20–27.86). Overall, serious adverse events were not significantly associated with antioxidant therapy compared with placebo (3 trials, 557 participants; RR 1.06; 95% CI: 0.84–1.32).

What are the findings based on?

Ten trials, with sample sizes that ranged from 30 to 993 participants. Six trials were single-centre and four multicentre, conducted in some or all of North and South America, India, Israel, and Europe. Two trials assessed the effects of vitamin E in haemodialysis patients and in patients with 'renal insufficiency' (defined as creatinine ≥125 μmol/L), two assessed human recombinant superoxide dismutase in kidney transplant recipients, one trial assessed coenzyme Q10 in both dialysis and non-dialysis CKD patients, three trials assessed multi-antioxidant therapy in kidney transplant recipients, one trial assessed bardoxolone methyl in patients with CKD stage 3 and 4 (eGFR 20–45 mL/min per 1.73 m^2), and one trial assessed acetylcysteine in haemodialysis patients. The studies were published between 1993 and 2011.

Study methodological quality was varied but overall, there was insufficient reported information regarding randomization and allocation concealment procedures among the included studies. Eight included trials were assessed as either having uncertain risk or high risk of selection bias that originated from lack of allocation concealment. Six trials reported the use of double-blinding; however, only three explicitly reported double-blinding methodologies. Incomplete outcome data were addressed in eight studies. Outcome reporting was inconsistent across the identified trials which limited the inclusion of data in the meta-analysis.

Implications for practice

- Overall, antioxidant therapy does not reduce the risk of cardiovascular disease or all-cause mortality
- There is evidence to suggest that the effect of antioxidant therapy varies according to CKD stage and that some benefit is seen for people on dialysis, where the risk of cardiovascular disease is significantly reduced
- Antioxidant therapy provides significant renal benefits for people with CKD 3 and 4 and kidney transplant recipients, including a significant reduction in the risk of ESKD, absolute reductions in serum creatinine levels, and improvements creatinine clearance
- Serious adverse events are not significantly increased by antioxidant therapy

Clinical perspective

This systematic review has shown that antioxidant therapy does not reduce the risk of death or cardiovascular events overall in CKD, but leaves open the possibility that there may be benefits in people with more advanced kidney failure. Additionally, there is important evidence to suggest that in

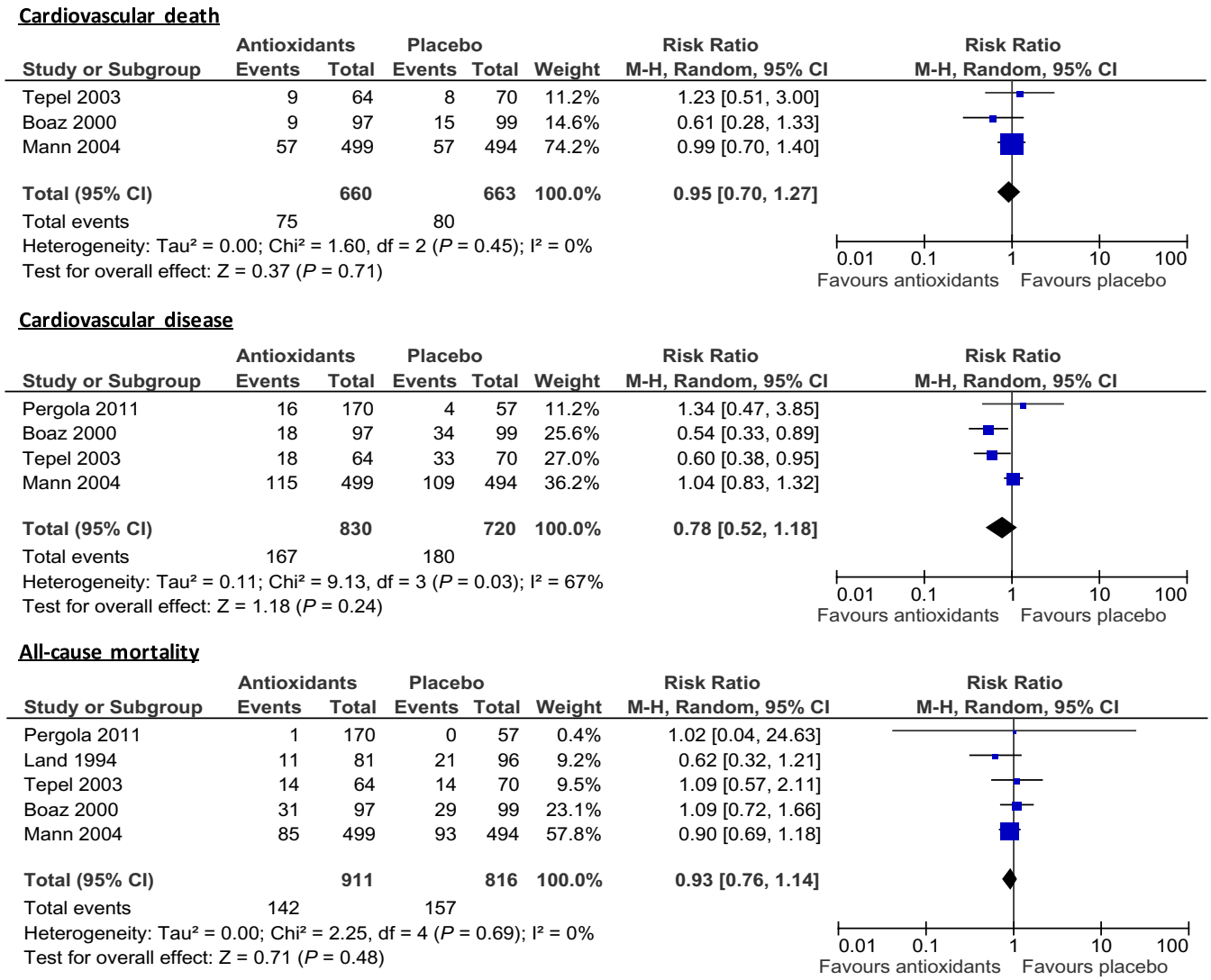

Fig. 1 Effect of antioxidant therapy on cardiovascular death, cardiovascular disease, and all-cause mortality in chronic kidney disease. CI, confidence interval.

CKD patients, antioxidant therapy may reduce the risk of progression to ESKD. Among trials, the consistently observed reductions in creatinine levels and improvements in kidney function support the plausibility of this observation.

The two trials in dialysis patients (Boaz 2000 and Tepel 2003) showed a 43% reduction in the risk of cardiovascular events, while trials including patients with moderate CKD showed no effect. A possible reason for the apparent greater benefit in dialysis patients may be that oxidative stress is particularly elevated in dialysis patients with cardiovascular disease compared with other patient groups. As such, it is possible that antioxidant therapy would have a greater effect in dialysis patients who have elevated oxidative stress and thus accelerated cardiovascular disease progression. However, it was also noted that based on quality assessment of the included trials, the two trials showing a beneficial effect of antioxidant therapy were generally of smaller size and poorer quality, with one trial being open-label. Therefore, there is a greater chance of bias in these trials, and thus a note of caution in interpretation, as these findings may be related to suboptimal trial conduct.

An additional important finding from this review is the observation that the risk of ESKD is significantly reduced with antioxidant therapy. It has been suggested that anti-inflammatory and antioxidant interventions may provide renal benefits in patients with CKD. This effect is further supported by the overall reduction in serum creatinine levels observed in people receiving antioxidant therapy. The available data suggest that these kidney function benefits of antioxidant therapy may translate into long-term benefits for major kidney outcomes. There was no clear evidence of harm observed among the trials of antioxidants in CKD patients; however, assessment was limited by a lack of consistent reporting or standardized outcomes by the included trials.

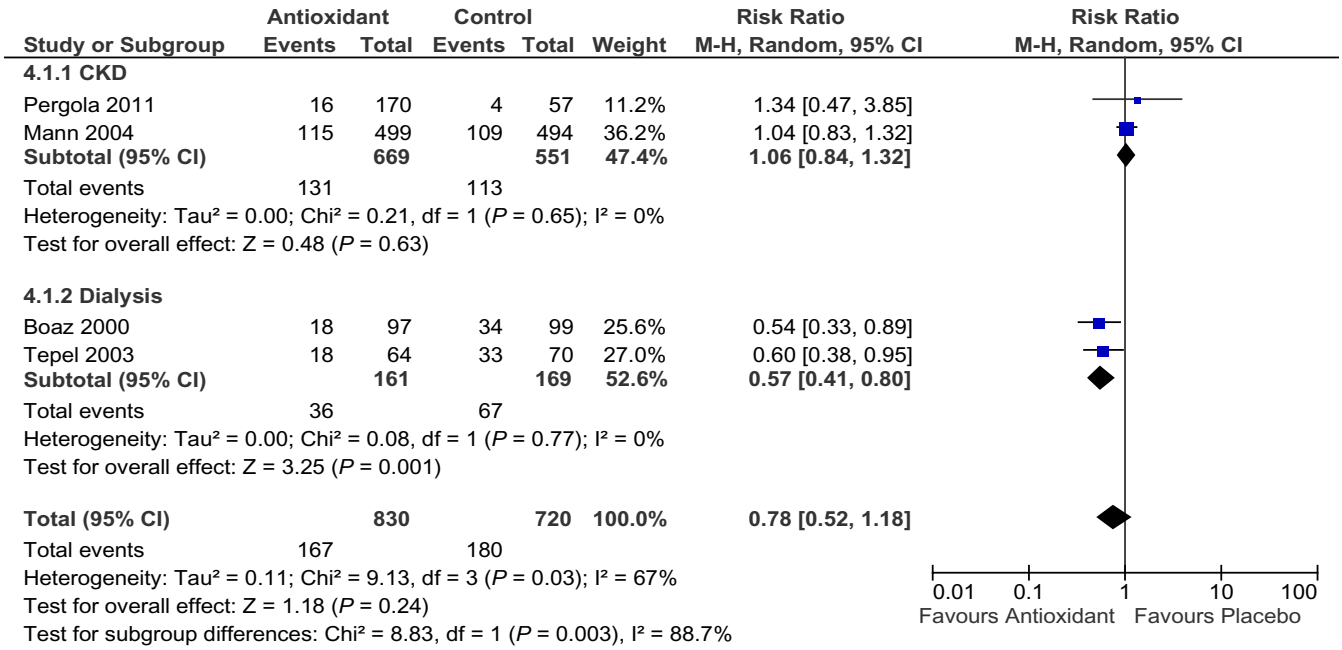

Fig. 2 Effect of antioxidant therapy on cardiovascular disease by CKD stage; CKD group included people with CKD stages 2–4 (eGFR between 20 and 45 mL/min per 1.73 m^2 for Pergola 2011 and creatinine ≥125 μmol/L for Mann 2004). CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Taken together, these findings provide a strong rationale for new properly powered trials to be conducted in the CKD population, particularly in individuals with more advanced kidney dysfunction as there is evidence to suggest greater benefit from antioxidant therapy in this group. Such trials are needed to confirm if antioxidant therapy could confer both renal and cardiovascular benefits in people with CKD.

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