The effect of folic acid based homocysteine lowering on cardiovascular events in people with kidney disease: systematic review and meta-analysis


CRD summary
The authors concluded that folic acid based homocysteine lowering therapy did not reduce cardiovascular events in people with kidney disease, and should not be used as a preventive treatment. Overall, this was a well-conducted review and the conclusion is likely to be reliable.

Authors' objectives
To evaluate the effect of folic acid based homocysteine lowering on cardiovascular outcomes in people with kidney disease.

Searching
MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1950 to June 2011. Search terms were reported. The reference lists of included trials and review articles were searched and ClinicalTrials.gov was accessed to locate additional studies. Original data were requested from authors/principal investigators, where necessary. There were no language restrictions.

Study selection
Eligible for inclusion were randomised controlled trials that evaluated folic acid based homocysteine lowering therapy compared with different doses, placebo or usual care in people with kidney disease. Trials had to have a minimum of 100 patient years of follow-up. Sequential or crossover trial designs were excluded. Participants could be in receipt of maintenance dialysis or a functioning kidney transplant. The primary outcome of interest was cardiovascular events (myocardial infarction, stroke and cardiovascular death). Secondary outcomes of interest were all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, leg amputation, dialysis access thrombosis and the start of renal replacement therapy in people not requiring dialysis. Adverse events were also analysed.

Included participants had chronic and/or end-stage kidney disease or a functioning kidney transplant. Sixty-four percent (median) were men (range 50 to 98%). The mean age of participants ranged from 48.5 to 72.2 years; average (median) proportion with a diagnosis of diabetes was 40% (range 11 to 100%); average (median) proportion with a history of cardiac disease was 34% (range 11 to 100%). Daily oral folic acid supplementation ranged from 2.5mg to 40mg; some trials included additional supplementation with Vitamin B.

Two reviewers independently selected the trials for inclusion.

Assessment of study quality
Trial quality was assessed on the following criteria: allocation concealment; blinding of outcome assessors, care providers and participants; completeness of study and follow-up; and use of intention-to-treat analysis.

Two reviewers independently carried out the quality assessment. Disagreements were resolved by consensus or by involving a third reviewer.

Data extraction
Intention-to-treat data were extracted to enable the presentation of relative risks (RR) and 95% confidence intervals (CI).

Two reviewers independently extracted the data. Disagreements were resolved by consensus or by involving a third reviewer.

Methods of synthesis
Effect sizes were combined in a random-effects meta-analysis. The $I^2$ statistic was used to quantify statistical
heterogeneity. Publication bias was assessed using a funnel plot. Various planned subgroup analyses were conducted.

**Results of the review**

Eleven trials (10,951 participants) were included in the review. Seven trials compared folic acid based homocysteine lowering therapy with placebo; one trial with usual care; and three trials with low dose folic acid/Vitamin B. Overall methodological quality was high (further details were reported). Follow-up ranged from 24 to 60 months (median 38 months).

There was no statistically significant effect of folic acid based homocysteine lowering therapy on cardiovascular events, overall and by disease classification. No significant heterogeneity was found. No significant effect was found for any of the secondary outcomes, or in any of the subgroup analyses. Reported across seven trials, adverse event rates ranged from 1.8% (leading to treatment withdrawal) to 89.1% (including dizziness, nausea and headache).

There was no evidence of publication bias.

**Authors’ conclusions**

Folic acid based homocysteine lowering therapy did not reduce cardiovascular events in people with kidney disease.

**CRD commentary**

The review question was clear and inclusion criteria were adequately specified to enable replication. Relevant data sources were accessed to locate published and unpublished studies, and steps were taken to minimise language bias. The review process was carried out with sufficient rigour to minimise error and bias and relevant quality assessment criteria were applied to the included trials. The method of synthesis and analysis of potential sources of heterogeneity were appropriate. The authors drew attention to limitations of the review, such as absence of individual patient data, variably defined chronic kidney disease and cardiovascular events, and possible selective reporting of people with kidney disease in the larger trials. Overall, this was a well-conducted review and the conclusion is likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that folic acid based homocysteine lowering therapy should not be used for the prevention of cardiovascular events in people with kidney disease.

**Research:** The authors did not state any specific recommendations for future research. However, they suggested that increased clarity and precision of effect might be provided from an analysis of individual patient data from all completed trials of folic acid based homocysteine lowering therapy.

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