EFFECT OF FOLIC ACID SUPPLEMENTATION ON CARDIOVASCULAR EVENTS IN NON-DIABETIC CHRONIC KIDNEY DISEASES: META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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OBJECTIVES

Homocysteine (Hcy) is viewed as a nontraditional marker of the prognosis of cardiovascular disease in the general population and in patients with chronic kidney disease (CKD). The effects of Hcy-lowering therapy in patients with CKD remain controversial. The aim of this study was to assess the effect of homocysteine (Hcy) lowering with folic acid on cardiovascular outcomes in people with CKD.

METHODS

We carried out a meta-analysis of published trials according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. A literature search was conducted with the following databases: PubMed, the Cochrane Controlled Clinical Trials Register Database and Nephrology Filters to June 2012.

Randomized trials, which include CKD patients who took more than 12 months of folic acid based Hcy-lowering therapy, were selected and the effects of interventions on cardiovascular outcomes were assessed. No language restriction was applied. Two authors independently extracted the data and reached a consensus on all of the items.

The endpoints included cardiovascular event (CVD), all-cause mortality, stroke and myocardial infarction (MI). The effects of folic acid based Hcy-lowering therapy on the outcomes were assessed by a meta-analysis using random effects models. Among thirty-nine studies reviewed, 13-studies (n = 11,106) that met our inclusion criteria were included in the meta-analysis (Figure 1).

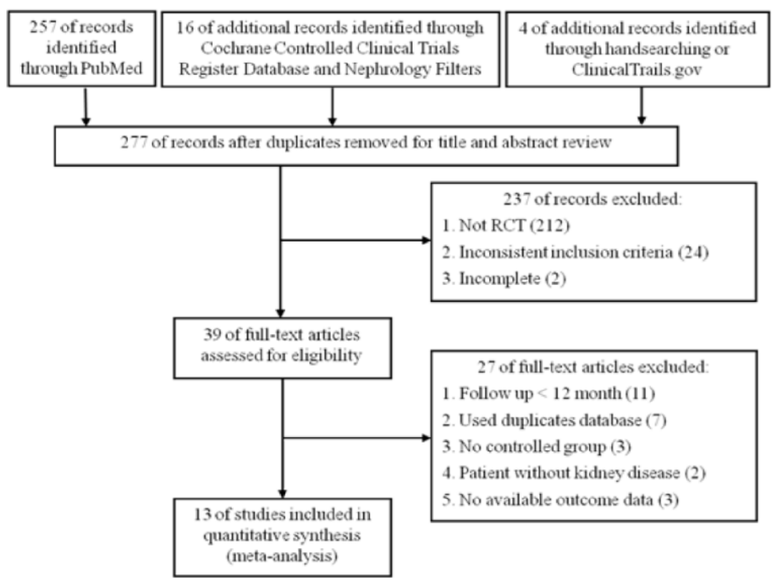

Figure 1. Flow diagram of identification process for eligible studies in this study.
RCT: randomized controlled trial

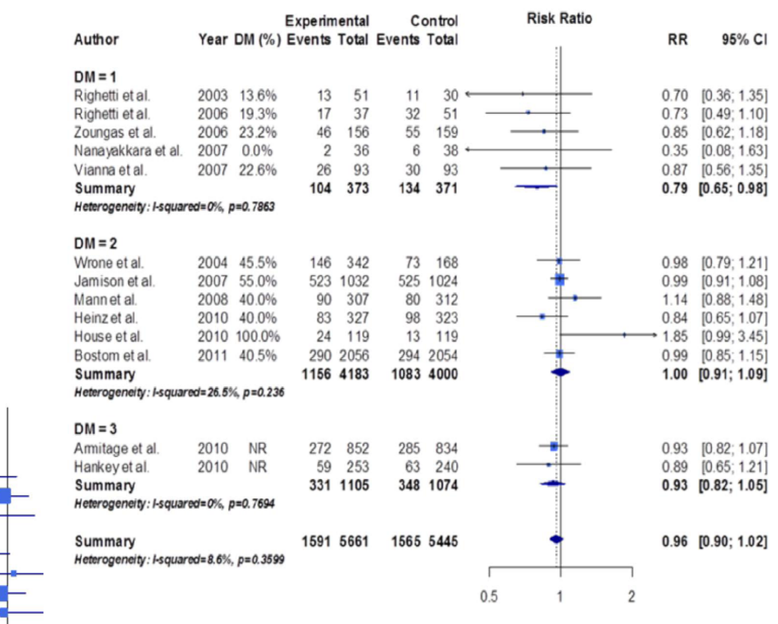

Figure 2. Subgroup analyses by percentage of diabetes mellitus in study population.
DM = 1: Less than 30 percent of the patients with DN; DM = 2: More than 30 percent of the patients with DN; DM = 3: Paper didn't show.

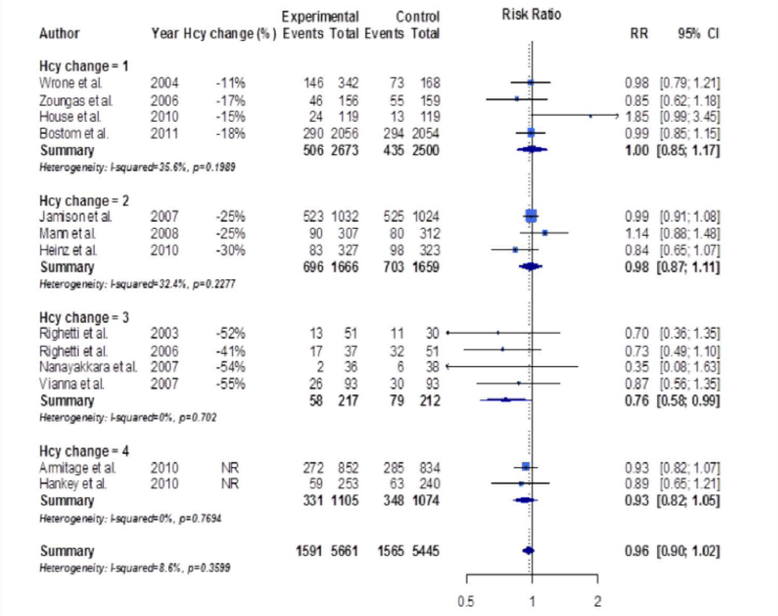

Figure 3. Subgroup analyses by homocysteine percentage change after Hcy-lowering therapy. Hcy change = 1: < 20%; Hcy change = 2: 20% - 30%; Hcy change = 3: > 30%; Hcy change = 4: Paper didn't show.

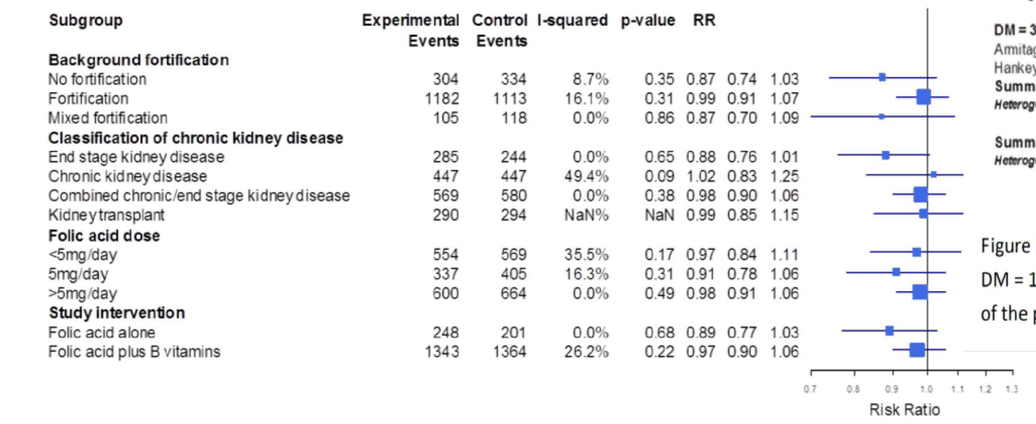

Figure 4. Subgroup analyses by food fortification policy, category of kidney disease, folic acid dose and intervention medications.
NaN%: A single study alone.

RESULTS

Folic acid based Hcy-lowering therapy did not prevent CVD (RR = 0.96, 95% CI = 0.90 - 1.02, I^2 = 8.6%) or any of the outcomes (Figure 2). In subgroup analyses, in the study groups which include less than 30 percent of the patients with diabetes mellitus (DM), the use of folic acid was associated with a 21% reduction in risk of cardiovascular events when compared with controls (RR = 0.79, 95% CI = 0.65 - 0.98, I^2=0%, Figure 3). A large decrease in Hcy levels (> 30%) from pre-treatment level was associated with a significant (24%) reduction in risk of CVD when compared with controls (RR = 0.76, 95% CI = 0.58-0.99; I^2 = 0%, Figure 3). In predefined subgroup analyses of background folic acid fortification condition (fortification, no fortification or mix fortification), study in no fortification groups revealed a potential therapeutic beneficial effect on CVD (RR =0. 87, 95%CI =0.74-1.03, p=0. 35) when compared with fortification groups (Figure 4).

CONCLUSIONS

Folic acid based Hcy-lowering therapy did not prevent cardiovascular events or any of the outcomes. DM may contribute the resistant to Hcy-lowering therapy in CKD patients. The response to Hcy-lowering therapy may also be influenced by mandatory folic acid fortification measures. In addition, reducing Hcy levels by more than 30% has beneficial effects on CVD risk regardless of folic acid fortification.

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