Interventions for lowering plasma homocysteine levels in dialysis patients

Nigwekar, Sagar; Kang, Amy; Zoungas, Sophia; Cass, Alan; Gallagher, Martin; Kulshrestha, Satyarth; Navaneethan, Sankar; Perkovic, Vlado; Strippoli, Giovanni; Jardine, Meg

Published in:
Cochrane Database of Systematic Reviews

DOI:
10.1002/14651858.CD004683.pub4

Published: 31/05/2016

Document Version
Publisher's PDF, also known as Version of record

Cochrane Library

Cochrane Database of Systematic Reviews

Interventions for lowering plasma homocysteine levels in dialysis patients (Review)

Nigwekar SU, Kang A, Zoungas S, Cass A, Gallagher MP, Kulshrestha S, Navaneethan SD, Perkovic V, Strippoli GFM, Jardine MJ

Nigwekar SU, Kang A, Zoungas S, Cass A, Gallagher MP, Kulshrestha S, Navaneethan SD, Perkovic V, Strippoli GFM, Jardine MJ.
Interventions for lowering plasma homocysteine levels in dialysis patients.
Cochrane Database of Systematic Reviews 2016, Issue 5. Art. No.: CD004683.
DOI: 10.1002/14651858.CD004683.pub4.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Interventions for lowering plasma homocysteine levels in dialysis patients

Sagar U Nigwekar[1], Amy Kang[2,3], Sophia Zoungas[4], Alan Cass[3,5], Martin P Gallagher[3], Satyarth Kulshrestha[6], Sankar D Navaneethan[7], Vlado Perkovic[3], Giovanni FM Strippoli[8,9,10,11,12], Meg J Jardine[3,13]

[1]Division of Nephrology, Massachusetts General Hospital, Scholars in Clinical Sciences Program, Harvard Medical School, Boston, MA, USA. [2]Sydney Medical School, The University of Sydney, Sydney, Australia. [3]Renal and Metabolic Division, The George Institute for Global Health, The University of Sydney, Camperdown, Australia. [4]Diabetes and Vascular Research Program, Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University, Clayton, Australia. [5]Menzies School of Health Research, Casuarina, Australia. [6]Department of Nephrology, University of Iowa Carver College of Medicine, Iowa City, IA, USA. [7]Baylor College of Medicine, Houston, Texas, USA. [8]Cochrane Kidney and Transplant, Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, Australia. [9]Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy. [10]Medical Scientific Office, Diaverum, Lund, Sweden. [11]Diaverum Academy, Bari, Italy. [12]Sydney School of Public Health, The University of Sydney, Sydney, Australia. [13]Department of Renal Medicine, Concord Repatriation General Hospital, Concord, Australia

Contact address: Sagar U Nigwekar, Division of Nephrology, Massachusetts General Hospital, Scholars in Clinical Sciences Program, Harvard Medical School, Boston, MA, USA. sagarnigs@gmail.com. snigwekar@partners.org.

Editorial group: Cochrane Kidney and Transplant Group.
Publication status and date: New, published in Issue 5, 2016.
Review content assessed as up-to-date: 25 January 2016.

Citation: Nigwekar SU, Kang A, Zoungas S, Cass A, Gallagher MP, Kulshrestha S, Navaneethan SD, Perkovic V, Strippoli GFM, Jardine MJ. Interventions for lowering plasma homocysteine levels in dialysis patients. *Cochrane Database of Systematic Reviews* 2016, Issue 5. Art. No.: CD004683. DOI: 10.1002/14651858.CD004683.pub4.

ABSTRACT

Background

People with end-stage kidney disease (ESKD) have high rates of cardiovascular events. Randomised controlled trials (RCTs) of homocysteine-lowering therapies have not shown reductions in cardiovascular event rates in the general population. However, people with kidney disease have higher levels of homocysteine and may have different mechanisms of cardiovascular disease. We performed a systematic review of the effect of homocysteine-lowering therapies in people with ESKD.

Objectives

To evaluate the benefits and harms of established homocysteine lowering therapy (folic acid, vitamin B_6, vitamin B_{12}) on all-cause mortality and cardiovascular event rates in patients with ESKD.

Search methods

We searched Cochrane Kidney and Transplant's Specialised Register to 25 January 2016 through contact with the Information Specialist using search terms relevant to this review.

Selection criteria

Studies conducted in people with ESKD that reported at least 100 patient-years of follow-up and assessed the effect of therapies that are known to have homocysteine-lowering properties were included.

Data collection and analysis

Two authors independently extracted data using a standardised form. The primary outcome was cardiovascular mortality. Secondary outcomes included all-cause mortality, incident cardiovascular disease (fatal and nonfatal myocardial infarction and coronary revascularisation), cerebrovascular disease (stroke and cerebrovascular revascularisation), peripheral vascular disease (lower limb amputation), venous thromboembolic disease (deep vein thrombosis and pulmonary embolism), thrombosis of dialysis access, and adverse events. The effects of homocysteine-lowering therapies on outcomes were assessed with meta-analyses using random-effects models. Prespecified subgroup and sensitivity analyses were conducted.

Main results

We included six studies that reported data on 2452 participants with ESKD. Interventions investigated were folic acid with or without other vitamins (vitamin B_6, vitamin B_{12}). Participants' mean age was 48 to 65 years, and proportions of male participants ranged from 50% to 98%.

Homocysteine-lowering therapy probably leads to little or no effect on cardiovascular mortality (4 studies, 1186 participants: RR 0.93, 95% CI 0.70 to 1.22). There was no evidence of heterogeneity among the included studies (I^2 = 0%). Homocysteine-lowering therapy had little or no effect on all-cause mortality or any other of this review's secondary outcomes. All prespecified subgroup and sensitivity analyses demonstrated little or no difference. Reported adverse events were mild and there was no increase in the incidence of adverse events from homocysteine-lowering therapies (3 studies, 1248 participants: RR 1.12, 95% CI 0.51 to 2.47; I^2 = 0%). Overall, studies were assessed as being at low risk of bias and there was no evidence of publication bias.

Authors' conclusions

Homocysteine-lowering therapies were not found to reduce mortality (cardiovascular and all-cause) or cardiovascular events among people with ESKD.

PLAIN LANGUAGE SUMMARY

Interventions for lowering plasma homocysteine levels in dialysis patients

Background

People with advanced kidney disease frequently develop heart disease, which is the most common cause of deaths in these people. An increased level of the amino acid (homocysteine) in the blood is a risk factor for heart disease in people with advanced kidney disease. Therapies that reduce homocysteine levels (e.g. folic acid, vitamins B_6 and B_{12}) are often used, but the benefits and harms of their use are unclear. We aimed to assess the benefits and harms of homocysteine-lowering therapies in people with advanced kidney disease who were on dialysis.

Study characteristics

From a search of the literature in January 2016, we identified six randomised controlled trials that involved 2452 participants aged between 48 and 65 years to be analysed.

Key results

We found that homocysteine-lowering therapies had no benefits for heart health in people with advanced kidney disease who were on dialysis. These therapies did not achieve any reduction in rates of heart disease-related death. However, homocysteine-lowering therapies were generally well tolerated, and had a mild side effect profile.

Quality of the evidence

Overall, studies were assessed as high quality.

BACKGROUND

Description of the condition

Dialysis-dependent end-stage kidney disease (ESKD) patients have reduced life expectancy, with annual mortality of 14.8% in Australia (McDonald 2007), and 16.7% in the USA (USRDS 2007). Chronic kidney disease (CKD) is an independent and powerful risk factor for cardiovascular disease (Go 2004; Weiner 2004). Cardiovascular mortality is significant in CKD (de Jager 2009). For dialysis-dependent ESKD patients, death from cardiovascular disease is 10 to 100 times higher than in age and sex-matched controls (Foley 1998).

The increased prevalence of cardiovascular disease among ESKD patients is not completely accounted for by the presence of traditional risk factors such as hypertension, dyslipidaemia, diabetes mellitus, smoking, and left ventricular hypertrophy (Baigent 2000). Thus, there has been increasing investigation of nontraditional risk factors such as anaemia, hyperparathyroidism and hyperhomocysteinaemia.

Description of the intervention

Homocysteine is an amino acid produced from the metabolism of methionine. It is believed to play a role in the pathogenesis of atherosclerosis by damaging the endothelium and promoting clotting (Eikelboom 1999). Epidemiological studies have shown homocysteine to be an independent risk factor for cardiovascular disease (HSC 2002). Elevated homocysteine level is a predictor of vascular disease including stroke, myocardial infarction (MI, heart attack), atherosclerosis (thickening of artery walls), arterial and venous thrombosis (clotting) and cardiovascular death in the general population (HSC 2002; Wald 2002) and in people with ESKD (Chauveau 1993; Moustapha 1998; Robinson 1996).

In contrast to the well-documented association between homocysteine levels and vascular events in the general population, the association between homocysteine levels and risk for atherothrombotic disease is not consistent among the ESKD population. Some investigators have described an inverse association between homocysteine levels and clinical outcomes in the ESKD patients with low levels of homocysteine being associated with worse outcomes (Kalantar-Zadeh 2004; Wrone 2001). However, even a mild increase in the homocysteine level appears to be a vascular risk factor in the general population and there is high prevalence of hyperhomocysteinaemia in ESKD. Thus, the paradoxical reverse association between homocysteine and clinical outcome in ESKD patients does not as such refute a possible role for homocysteine in the vascular pathogenesis. Furthermore, it has also been shown that association of hyperhomocysteinaemia and worse clinical outcomes persists in ESKD patients without chronic inflammation-malnutrition state (Ducloux 2006). These authors postulate that the burden of chronic inflammation-malnutrition might mask the true relationship between hyperhomocysteinaemia and cardiovascular risk among dialysis-dependent ESKD patients.

How the intervention might work

Because kidney metabolism is the primary means by which homocysteine is cleared, plasma homocysteine has a strong inverse correlation with estimated glomerular filtration rate (Freidman 2001). Among patients with ESKD, the prevalence of hyperhomocysteinaemia is 85% to 100% (Bostom 1999).

In classical homocystinuria, plasma total homocysteine concentrations are very high (100 to 400 μmol/L), and untreated patients die prematurely from venous thromboembolism and malignant arterial disease. Long-term treatment aimed at lowering homocysteine levels has been extremely effective in reducing the potentially life-threatening vascular risk in these patients modified by agents that lower homocysteine such as folic acid and vitamins B_6 and B_{12}. Of the homocysteine-lowering therapies, folic acid is the most effective and consistent in reducing homocysteine levels in ESKD (van Guldener 2006).

Why it is important to do this review

A limited number of studies of homocysteine-lowering therapy in ESKD patients have been conducted which individually have been unable to find a statistically significant effect on surrogate markers of cardiovascular disease, cardiovascular events or all-cause mortality (ASFAST 2004; HOST Study 2004; Vianna 2007; Wrone 2004). The picture is confused by the inability of studies to normalise homocysteine levels in most patients, despite the administration of larger doses of folic acid than in studies of other population groups (ASFAST 2004; Gonin 2005).

Although there is no RCT evidence to support folic acid or vitamin B interventions, multivitamin supplementation for patients with ESKD is commonly practiced. The K/DOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients promote the administration of folate, vitamins B_6 and B_{12} to compensate for dialysate losses and prevent elevation of homocysteine on the grounds of cardiovascular risk (K/DOQI 2005). The group also acknowledged the lack of evidence in the area and state that further data are required regarding the effect of vitamin therapy on clinical outcomes. Furthermore potential harms associated with folic acid supplements have not been excluded (Zoccali 2010).

In light of the burden of cardiovascular disease for patients with ESKD, the effectiveness or otherwise of any potentially effective interventions needs to be clearly established. This review aimed to assess the benefits and harms of homocysteine lowering therapy among people with ESKD to guide decision making and improve outcomes for patients.

OBJECTIVES

To evaluate the benefits and harms of established homocysteine lowering therapy (folic acid, vitamin B_6, vitamin B_{12}) on all-cause mortality and cardiovascular event rates in patients with ESKD.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alteration, use of alternate medical records, date of birth or other predictable methods) looking at the use of established homocysteine lowering therapy, with a minimum of 100 patient years were included to reduce the risk of reporting or publication bias. Sequential and cross-over studies were excluded.

Types of participants

We included adults (aged over 18 years) with ESKD defined as those requiring maintenance dialysis. Patients with functioning kidney transplants were excluded.

Types of interventions

Studies randomising patients to therapies which have proven efficacy in lowering homocysteine levels were included. Studies of regimens in which the main mechanism of action is thought not to be homocysteine lowering were excluded (e.g. simvastatin plus folic acid, N-acetyl cysteine). We investigated the following comparisons.

- Homocysteine-lowering therapy versus placebo or usual care
- Higher dose homocysteine-lowering therapy versus lower dose homocysteine-lowering therapy
- Any schedule of treatment
- Any route of treatment.

Types of outcome measures

Primary outcomes

- Cardiovascular mortality

Secondary outcomes

- All-cause mortality
- Cardiovascular disease
  - Fatal and nonfatal MI
  - Coronary revascularisation
- Cerebrovascular disease
  - Stroke
  - Cerebrovascular revascularisation
- Peripheral vascular disease and venous thromboembolic disease
  - Lower limb amputation
  - Deep vein thrombosis (DVT) and pulmonary embolism (PE)
- Kidney-specific outcomes
  - Thrombosis of dialysis access
- Adverse events from folic-based therapy
  - Gastrointestinal events
  - Dermatological events
  - Neurological events
  - Malignancy incidence and mortality
  - Any self-reported adverse events.

Search methods for identification of studies

Electronic searches

We searched Cochrane Kidney and Transplant's Specialised Register to 25 January 2016 through contact with the Information Specialist using search terms relevant to this review. The Specialised Register contains studies identified from the following sources.

1. Quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies as well as a list of handsearched journals, conference proceedings and current awareness alerts are available in the Specialised Register section of information about the Cochrane Kidney and Transplant.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Steps in data collection and analyses are outlined below.

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies that may be relevant to the review. Titles and abstracts were screened independently by two authors, and studies that were not applicable were discarded. However, studies and reviews that might include relevant data or information on studies were retained initially. Two authors independently assessed retrieved abstracts and the full text as necessary of these studies to determine which studies satisfy the inclusion criteria.

Data extraction and management

Data extraction was carried out independently by two authors using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of one RCT existed, only the publication with the most complete data were to be included; however, we did not find any duplicate publications. Disagreements were resolved by consultation.

Assessment of risk of bias in included studies

The following items were independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
    - Participants and personnel (performance bias)
    - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes (all-cause mortality, MI, coronary revascularisation, cardiovascular death, stroke, cerebrovascular revascularisation, lower limb amputation, thrombosis of arteriovenous (AV) access, DVT, PE), results were expressed as risk ratio (RR) with 95% confidence intervals (CI). Data were pooled using the random-effects model but the fixed-effect model was also analysed to ensure robustness of the model chosen and susceptibility to outliers.

Dealing with missing data

Any further information required from the original author was to be requested by written correspondence and any relevant information obtained in this manner was included in the review. Attrition rates, such as drop-outs, losses to follow-up and withdrawals were to be investigated. Issues of missing data and imputation methods (e.g. last-observation-carried-forward) were to be critically appraised (Higgins 2011).

Assessment of heterogeneity

Heterogeneity was analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

Publication bias was assessed using a funnel plot (Egger 1997). Attrition bias was assessed using the loss/event ratio.

Data synthesis

Data were pooled using the random-effects model but the fixed-effect model was also analysed to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were conducted to explore possible sources of heterogeneity using inverse variance according to the following characteristics.

- Study intervention
- Exposure to folic acid among control group participants
- Proportion of participants with diabetes mellitus
- Proportion of participants with cardiac disease
- Study duration follow-up
- Study event number.

We aimed to analyse the ability of interventions to normalise homocysteine levels in a subgroup of studies that enrolled patients with elevated homocysteine levels. Plausible explanations for variations in treatment effect were explored using subgroup analyses based on study quality and length of follow-up.

Sensitivity analysis

Sensitivity analyses were conducted to ensure conclusions are robust to decisions made during the review process such as inclusion criteria and imputing of missing data. Where outcomes sought were reported in insufficient detail to allow meta-analysis and further information was not forthcoming from triallists, we planned to summarise these outcomes and assess with descriptive techniques.

We planned to calculate the number of persons needed to treat to avoid one cardiovascular death if adequate data were available; however, our non-significant results did not permit making this calculation.

RESULTS

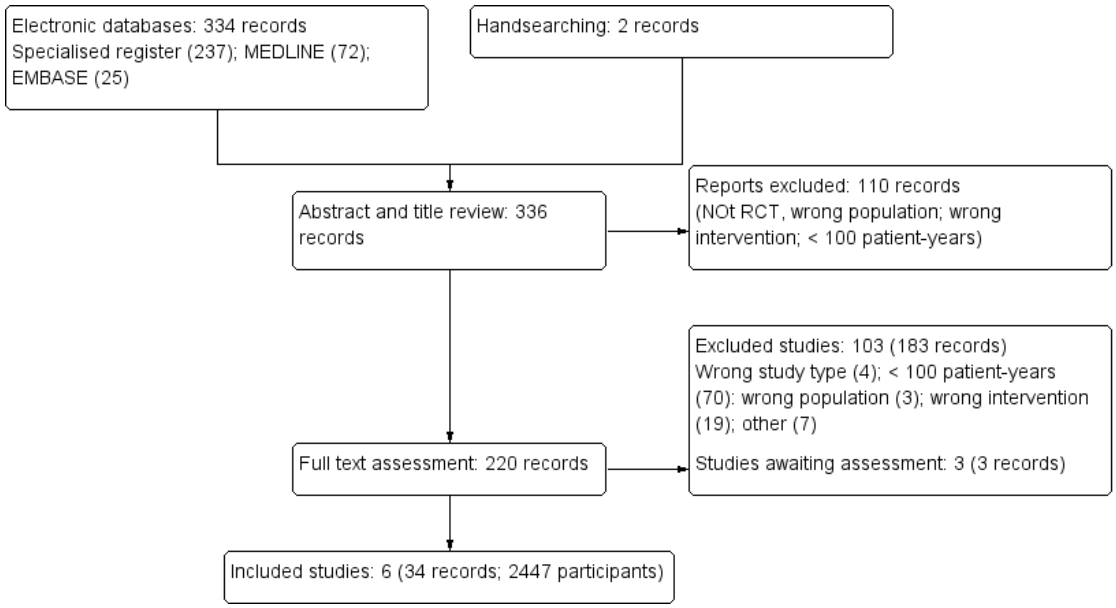
Description of studies

Detailed description of study search results and description of studies is outlined below.

Results of the search

We searched Cochrane Kidney and Transplant's Specialised Register to 25 January 2016 through contact with the Information Specialist using search terms relevant to this review. Additionally, reference lists of review articles, relevant studies and clinical practice guidelines were also searched. This comprehensive search yielded 336 records. The titles and abstracts of these 336 records were assessed and 110 articles were excluded since they did not meet the prespecified review criteria. The full texts of the remaining 220 records were reviewed; six studies (34 records) met our review criteria (Figure 1). Prior to publication three additional studies were identified and these will be assessed in a future update of this review (NCT00004495; Soleimani 2011; Tayebi-Khosroshahi 2013).

Figure 1. Flow diagram showing study selection



Included studies

We included six studies that involved 2452 participants with ESKD requiring dialysis (ASFAST 2004; Heinz 2009; HOST Study 2004; Righetti 2003; Vianna 2007; Wrone 2004). All studies were reported between 2003 and 2009.

Design

All included studies were parallel RCTs (ASFAST 2004; Heinz 2009; HOST Study 2004; Righetti 2003; Vianna 2007; Wrone 2004). Five studies were double-blinded (ASFAST 2004; Heinz 2009; HOST Study 2004; Vianna 2007; Wrone 2004) and one

study followed an open-label design (Righetti 2003).

Sample sizes

Sample sizes of included studies ranged from 88 participants (Righetti 2003) to 761 participants (HOST Study 2004).

Setting

The included studies were conducted in outpatient dialysis units (ASFAST 2004; Heinz 2009; HOST Study 2004; Righetti 2003; Vianna 2007; Wrone 2004). Two were single centre studies (Righetti 2003; Vianna 2007) and four were multicentre studies (ASFAST 2004; Heinz 2009; HOST Study 2004; Wrone 2004). Studies were conducted in the USA (HOST Study 2004; Wrone 2004), Australia and New Zealand (ASFAST 2004), Germany (Heinz 2009), Brazil (Vianna 2007) and Italy (Righetti 2003). Mandatory folate fortification was present only in the USA at the time the studies were conducted. Three studies included ESKD patients on maintenance haemodialysis (Heinz 2009; Righetti 2003; Vianna 2007) only. Three studies included ESKD patients on both maintenance haemodialysis and peritoneal dialysis (ASFAST 2004; HOST Study 2004; Wrone 2004). Proportions of peritoneal dialysis patients were 28% (ASFAST 2004), 8.2% (Wrone 2004) or not reported (HOST Study 2004).

Participants

The mean age of study participants was between 48 and 65 years (Characteristics of included studies). The proportion of study participants who were male ranged from 50% to 98%, the proportion with a diagnosis of diabetes mellitus ranged from 19% to 55%, and the proportion with a history of cardiac disease ranged from 11% to 58%. Follow-up ranged from 2.0 to 3.6 years. Participants consisted entirely of people with ESKD in four studies (Heinz 2009; Righetti 2003; Vianna 2007; Wrone 2004) and both ESKD and CKD in two studies (ASFAST 2004; HOST Study 2004). Specific outcome data on ESKD patients were obtained from the study authors of ASFAST 2004.

Interventions

Interventions investigated were folic acid with or without other vitamins (vitamin B_6, vitamin B_{12}). The dose of folic acid was variable from the equivalent daily dose of 5 mg to 40 mg. Wrone 2004 compared placebo versus low dose (5 mg) versus high dose (15 mg) folate therapy with the latter two arms combined for the purposes of this review. Comparator treatment was placebo (ASFAST 2004; HOST Study 2004; Vianna 2007), low dose folic acid (Heinz 2009; Wrone 2004) or usual care (Righetti 2003).

Outcomes

For ASFAST 2004, the primary outcomes were change in rate of progression of mean maximum carotid artery intimal media thickness, composite of MI, stroke, and death from cardiovascular cause. Secondary outcomes were all fatal and nonfatal cardiovascular events including MI, stroke, unstable angina, revascularisation, and peripheral vascular disease.

The primary outcome in Heinz 2009 was overall mortality. Secondary outcomes were occurrence of first fatal or nonfatal cardiovascular event (MI, unstable angina, coronary vascularisation procedure, sudden cardiac death, stroke, peripheral artery disease, PE, and thromboses). Shunt thromboses were not regarded as an end point.

The primary outcome in HOST Study 2004 was time to death from any cause. Secondary outcomes were time to MI, stroke, amputation of all or part of a lower extremity, and a composite of these three plus all-cause mortality.

For Righetti 2003, the primary outcome was a composite cardiovascular end point (typical history of angina with abnormal myocardial scintigraphy or coronarography, fatal and nonfatal MI, symptomatic extracranial carotid stenosis resulting in carotid endarterectomy, fatal and nonfatal stroke and sudden cardiac arrest). There were no secondary outcomes.

The primary outcome in Vianna 2007 was a composite of new major cardiovascular events, including death from cardiovascular causes, nonfatal MI, cardiac arrhythmias, angina, heart failure, and cerebral vascular accident. Secondary outcome was the evaluation of the intima-media thickness of the common carotid arteries.

For Wrone 2004, the primary outcomes were cardiovascular events (coronary artery intervention, MI, stroke, transient ischaemic attack, carotid endarterectomy, limb amputation) and mortality. The secondary outcome was vascular access thrombosis (among those with AV fistulae).

Excluded studies

Excluded studies are described (Characteristics of excluded studies). Reasons for exclusion were: wrong study design (4 studies); less than 100 patient-years follow-up (70 studies); wrong study population (3 studies); not homocysteine-lowering interventions (19 studies); outcome data were not extractable (7 studies).

Risk of bias in included studies

A risk of bias graph and summary are presented in Figure 2 and Figure 3. Risk of selection bias related to random sequence generation and allocation concealment was low in 50% of the included studies. Risks attributed to performance, attrition, detection, and reporting biases were low in more than 65% of included studies.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

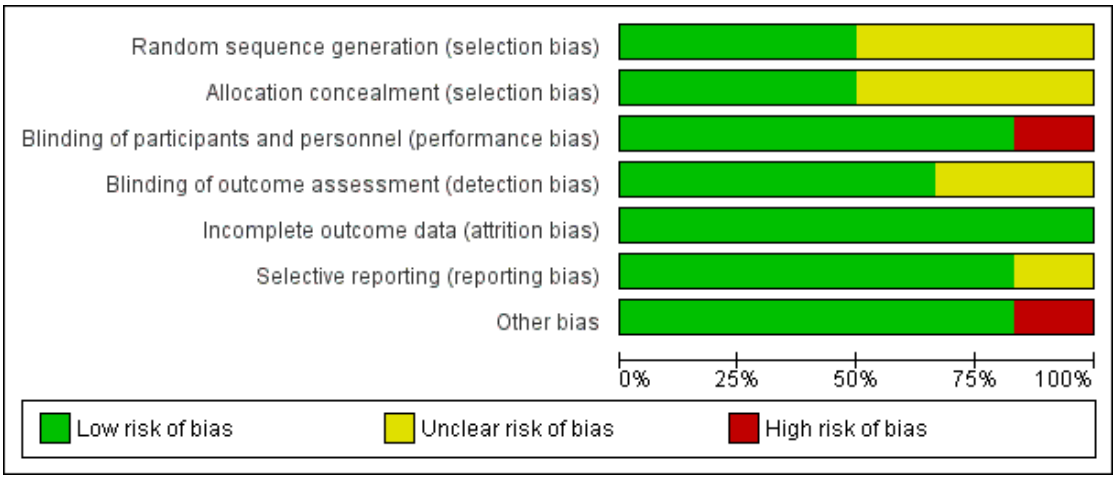
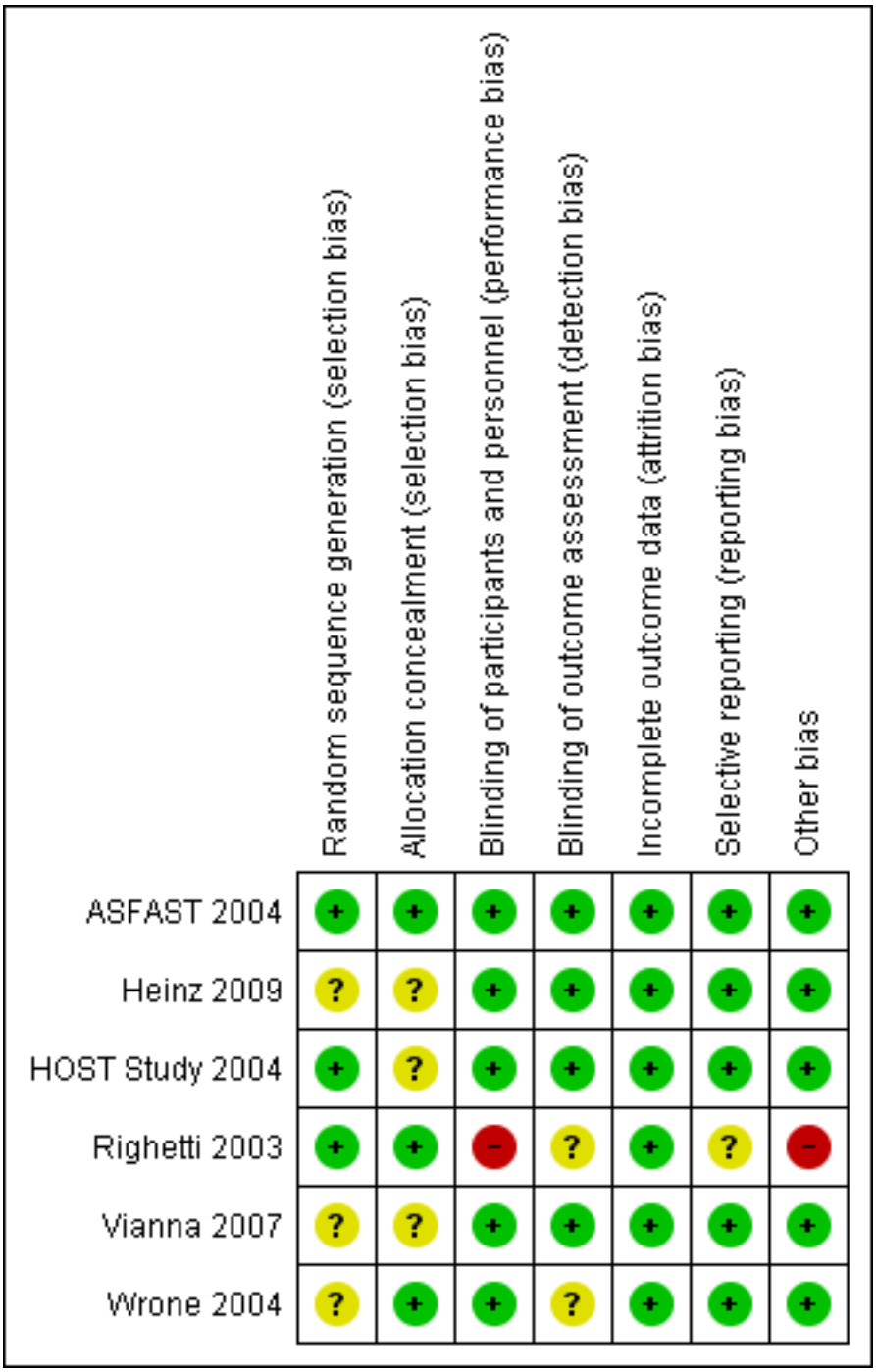


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Method of sequence generation was assessed as being at low risk of bias in three studies (ASFAST 2004; HOST Study 2004; Righetti 2003) and unclear in three studies (Heinz 2009; Vianna 2007; Wrone 2004).

Allocation concealment was assessed as being at low risk of bias in three studies (ASFAST 2004; Righetti 2003; Wrone 2004) and unclear in three studies (Heinz 2009; HOST Study 2004; Vianna 2007).

Blinding

Performance bias (participants and study staff) was assessed as low in five studies (ASFAST 2004; Heinz 2009; HOST Study 2004; Vianna 2007; Wrone 2004) and high in one study (Righetti 2003).

Detection bias (outcome assessors) was assessed as low in four studies (ASFAST 2004; Heinz 2009; HOST Study 2004; Vianna 2007) and unclear in two studies (Righetti 2003; Wrone 2004).

Incomplete outcome data

Attrition bias was assessed as low in all six studies.

Selective reporting

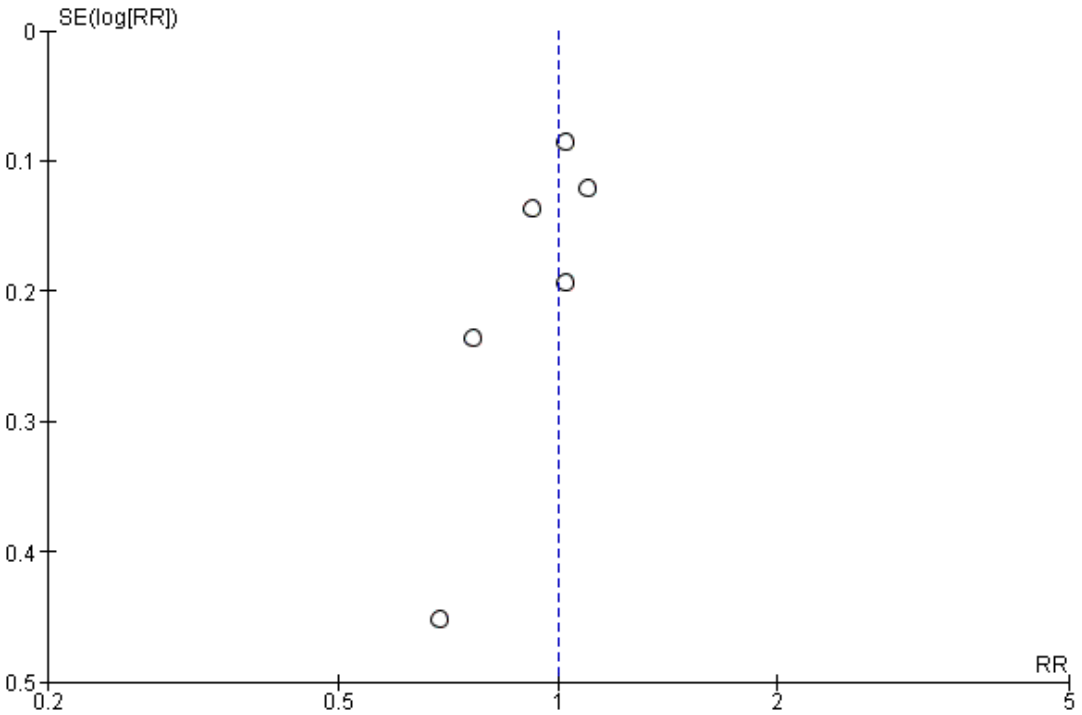
Reporting bias was assessed as low in five studies (ASFAST 2004; Heinz 2009; HOST Study 2004; Vianna 2007; Wrone 2004) and unclear in one study (Righetti 2003).

Other potential sources of bias

Righetti 2003 was assessed as being at high risk of other bias due to the imbalance between the groups in the baseline data; all other studies were assessed as being at low risk of other potential biases.

Funnel plot analysis did not show publication bias (Figure 4).

Figure 4. Funnel plot of comparison: 2 Secondary outcomes, outcome: 2.1 all-cause mortality



Effects of interventions

Primary outcomes

Cardiovascular mortality

Four studies (ASFAST 2004; Heinz 2009; Righetti 2003; Vianna 2007) reported 173 cardiovascular mortality events among 1186 participants. Homocysteine-lowering therapy had no overall effect on cardiovascular mortality (Analysis 1.1 (4 studies, 1186 participants): RR 0.93, 95% CI 0.70 to 1.22; I^2 = 0%). There was no evidence of heterogeneity.

We planned to calculate the number of persons needed to treat to avoid one cardiovascular death if adequate data were available; however, our non-significant results did not enable this calculation to be made.

Secondary outcomes

All-cause mortality

The six included studies reported 719 all-cause mortality events among 2447 participants. Homocysteine-lowering therapy had no overall effect on all-cause mortality (Analysis 2.1 (6 studies, 247 participants): RR 1.00, 95% CI 0.89 to 1.11; I^2 = 0%). There was no evidence of heterogeneity.

Fatal and nonfatal myocardial infarction

Four studies (ASFAST 2004; Heinz 2009; Righetti 2003; Wrone 2004) reported 75 fatal and nonfatal MI events among 1510 participants. Homocysteine-lowering therapy had no overall effect on MI (Analysis 2.2 (4 studies; 1510 participants): RR 1.04, 95% CI 0.66 to 1.62; I^2 = 0%). There was no evidence of heterogeneity.

Coronary revascularisation

Heinz 2009 and Wrone 2004 reported 44 coronary revascularisation events among 1160 participants. Homocysteine-lowering therapy had no overall effect on coronary revascularisation (Analysis 2.3 (2 studies, 1160 participants): RR 0.83, 95% CI 0.22 to 3.14; I^2 = 74%). Significant heterogeneity was observed.

Stroke

Four studies (ASFAST 2004; Heinz 2009; Righetti 2003; Wrone 2004) reported 77 stroke events among 1510 participants. Homocysteine-lowering therapy had no overall effect on stroke (Analysis 2.4 (4 studies, 1510 participants): RR 0.89, 95% CI 0.57 to 1.40; I^2 = 0%)). There was no evidence of heterogeneity.

Cerebrovascular revascularisation

Adequate data on this outcome were not available in published reports and further information was not forthcoming from the triallists.

Lower limb amputation

Adequate data on this outcome were not available in published reports and further information was not forthcoming from the triallists.

Deep vein thrombosis and pulmonary embolism

Heinz 2009 reported 13 DVT and PE events among 650 participants. Homocysteine-lowering therapy had no overall effect on DVT and PE (Analysis 2.5: RR 1.15, 95% CI 0.39 to 3.39).

Thrombosis of dialysis access

HOST Study 2004 and Wrone 2004 reported 533 dialysis access thrombosis events among 1261 participants. Homocysteine-lowering therapy had no overall effect dialysis access thrombosis (Analysis 2.6 (2 studies, 1261 participants): RR 1.00, 95% CI 0.88 to 1.14; I^2 = 0%). There was no evidence of heterogeneity.

Adverse events from folic acid-based therapy

Adverse event rates were reported in three studies (Heinz 2009; Righetti 2003; Wrone 2004, 1248 participants) where homocysteine-lowering therapy had no effect on adverse event rates (Analysis 2.7 (3 studies, 1248 participants): (RR 1.12, 95% CI 0.51 to 2.47; I^2 = 0%). Reported adverse events included nausea, abdominal discomfort, hunger and weight gain, skin rashes, headaches, fatigue, and paraesthesia. We were unable to complete planned separate analyses of gastrointestinal, dermatological, neurological and malignant events due to the small number of studies reporting these outcomes. Rate of withdrawal from study treatment due to adverse events was less than 1% among the included studies.

Subgroup analyses

Subgroup analyses were conducted to explore possible sources of heterogeneity according to the following characteristics.

Study intervention

The impact of intervention on cardiovascular events did not differ significantly (P = 0.649) when studies of folic acid alone (ASFAST 2004; Vianna 2007) were compared with studies of folic acid plus B group vitamins (Heinz 2009; Righetti 2003).

Exposure to folic acid among control group participants

The impact of intervention on cardiovascular events did not differ significantly (P = 0.557) when studies of low dose exposure in control group participants (Heinz 2009) were compared with studies of no low dose exposure in control group participants (ASFAST 2004; Righetti 2003; Vianna 2007).

Proportion of participants with diabetes mellitus

The impact of intervention on cardiovascular events did not differ significantly (P = 0.557) when studies that included more than a third of participants with diabetes mellitus (Heinz 2009) were compared with studies that included fewer than a third of participants with diabetes mellitus (ASFAST 2004; Righetti 2003; Vianna 2007).

Proportion of participants with cardiac disease

The impact of intervention on cardiovascular events did not differ significantly (P = 1.000) when studies that included more than a third of participants with cardiac disease (Heinz 2009; Righetti 2003) were compared with studies that included fewer than a third of participants with cardiac disease (ASFAST 2004; Vianna 2007).

Study follow-up duration

The impact of intervention on cardiovascular events did not differ significantly (P = 0.649) when studies with more than 30 month follow-up (ASFAST 2004) were compared with those that had with less than 30 months follow-up (Heinz 2009; Vianna 2007; Righetti 2003).

Study event number

The impact of interventions on cardiovascular events did not differ significantly (P = 0.557) when studies with more than 150 events (Heinz 2009) were compared with those that had fewer than 150 events (ASFAST 2004; Vianna 2007; Righetti 2003).

We aimed to analyse the ability of interventions to normalise homocysteine level in a subgroup of studies that enrolled patients with elevated homocysteine levels. However, there was only one study (Vianna 2007) in which a significant proportion of patients in the active arm achieved normalisation of homocysteine levels. In this study, there was no difference in cardiovascular mortality between active and control arm participants.

Sensitivity analyses

The same results were observed with fixed-effects and random-effects models.

Plausible explanations for variations in treatment effect for primary outcome were explored using subgroup analyses based on study quality and length of follow-up.

The impact of intervention on cardiovascular mortality did not differ significantly (P = 0.649 for heterogeneity) when studies with and without blinding of participants and study staff (ASFAST 2004; Heinz 2009; Vianna 2007) were compared.

The impact of interventions on cardiovascular mortality did not differ significantly (P = 0.657) when studies with median follow-up over three years (ASFAST 2004) were compared with median follow-up of fewer than three years.

DISCUSSION

Summary of main results

In this systematic review including 2452 participants with ESKD, randomisation to folic acid-based homocysteine-lowering therapy did not affect cardiovascular mortality, all-cause mortality, and incidence of cardiovascular events including MI, stroke, venous or access thrombosis. Null results were consistently observed across all prespecified subgroups and sensitivity analyses. Reported adverse events from these therapies were mild and rates of adverse events were variable across the studies. Overall, there was no evidence of harm defined by rates of adverse events in this population.

Overall completeness and applicability of evidence

Guidelines for ESKD patients routinely suggest supplementation with folic acid and B group vitamins (homocysteine-lowering therapies) without lack of clear evidence (K/DOQI 2005), and many people with ESKD appear to be receiving folic acid supplementation (Andreucci 2004). Our findings suggest that folic acid-based homocysteine-lowering should not be used for cardiovascular prevention in people with kidney disease, a population in whom medication burden is often high.

Quality of the evidence

The strengths of our systematic review we that an important clinical question has been investigated focusing on a study population with ESKD, using rigorous methodology and study search strategy techniques. We found consistent null results in primary, secondary, subgroup and sensitivity analyses.

These findings have direct implications for millions of people with ESKD globally who are currently taking homocysteine-lowering medications.

Risk of selection bias related to random sequence generation and allocation concealment was low in 50% of the included studies.

Risks attributed to performance, attrition, detection, and reporting biases were low in more than 65% of included studies.

Potential biases in the review process

Limitations of our systematic review include reliance on tabular rather than individual patient level data. We focused on cardiovascular mortality as our primary outcome; however, this outcome was reported in only four of the six included studies. Competing risks for cardiovascular mortality were not analysed. Although funnel plot analysis suggested a low possibility of publication bias, this cannot be excluded based on the small number of included studies. We could not conduct separate analyses for peritoneal and haemodialysis patients since adequate data were not available. Overall, participants from the included studies were younger than the average ESKD population and this may limit generalisability. Data on genetic polymorphisms that determine homocysteine-lowering effects of therapies (Klerk 2002) were not available; however, these polymorphisms have been shown to have no effects among dialysis patients (Aucella 2005). Nevertheless, although lowering of homocysteine levels were noted in all studies, normalisation of homocysteine levels was rare, pointing to the possibility of folic acid resistance in ESKD patients (Robinson 1996) and possible need for higher doses. However, in studies where high dose (> 5 mg daily) folic acid was administered, similar null effects on outcomes were noted (ASFAST 2004; HOST Study 2004; Wrone 2004).

Recent data indicate that there may be non-cardiovascular benefits of homocysteine lowering in the general population (such as reduced fracture risk) (Yang 2012) and our review did not evaluate effects on such outcomes.

Agreements and disagreements with other studies or reviews

Our findings were consistent with a recent meta-analysis conducted in the general population for cardiovascular mortality, all-cause mortality and MI (Huang 2012); however, our findings were discordant in terms of effects on stroke risk reduction.

Huang 2012 pooled data from 19 studies that included 47,921 participants and observed approximately 12% reduction in stroke risk in the general population. Although the analyses by Huang 2012 suffer from heterogeneity of patient populations in the pooled studies, other possible reasons for differences in stroke risk reduction between general and ESKD populations may relate to differences in biological risk factors for cerebrovascular disease in dialysis versus general populations (Kanbay 2010).

VITATOPS 2010 was conducted in patients who had experienced a recent stroke or transient ischaemic attack and found no significant difference for cardiovascular events (RR 0.91, 95% CI 0.82 to 1.00, P = 0.05) or stroke (RR 0.92, 95% CI 0.81 to 1.06).

There have been two recent meta-analyses that evaluated the effects of homocysteine lowering therapies on cardiovascular events in patients with kidney disease. Jardine 2012 included 11 studies comprising 4389 patients with CKD, 2452 with ESKD, and 4110 with functioning kidney transplants. In Jardine 2012, folic acid-based therapy did not reduce cardiovascular event incidence (RR 0.97, 95% CI 0.92 to 1.03, P = 0.326). Pan 2012 pooled 10 studies involving 4836 participants with CKD or ESKD. The investigators noted that the estimated relative risks were not significantly different for any cardiovascular outcomes and all-cause mortality.

Our findings were consistent with these findings. In addition, we specifically derived outcome data on ESKD patients from studies that involved both CKD and ESKD patients (ASFAST 2004; HOST Study 2004). Considering these differences, we believe that the findings of our review are likely to be a better estimate of the true effect of folic acid-based homocysteine-lowering on cardiovascular outcomes in ESKD patients. In combination with results from Jardine 2012 and Pan 2012 we feel confident regarding our conclusions on null effect from homocysteine-lowering therapies in ESKD patients and further solidify futility of such treatments as discussed in a recent editorial (Haynes 2012).

Recent data regarding associations between hyperhomocysteinaemia and cardiovascular risk (Menon 2006; Suliman 2007) have questioned the earlier findings that linked hyperhomocysteinaemia with increased cardiovascular risk (Robinson 1996) and thus further strengthen our conclusions. In fact, hyperhomocysteinaemia in ESKD may be an illustration of reverse epidemiology with some authors finding elevated homocysteine levels associated with reduced cardiovascular risk (Kalantar-Zadeh 2004) as has been described for factors such as obesity (Kalantar-Zadeh 2005) in the population with ESKD. Regardless of the nature of the association reported by observational studies, our results clearly indicate that interventions to lower homocysteine levels in people with ESKD do not offer cardiovascular risk reduction and are likely to be futile. We found one study listed at clinicaltrials.gov with unknown recruitment status on this topic (NCT00004495); however, the enrolment goal for this study is listed as 84 and it is unlikely to significantly affect results of our analyses.

AUTHORS' CONCLUSIONS

Implications for practice

In patients with ESKD, homocysteine-lowering therapies do not reduce mortality (cardiovascular and all-cause) or cardiovascular events. Homocysteine-lowering therapies should not be used in the ESKD population for cardiovascular risk reduction.

Implications for research

From this review and meta-analyses, we conclude that there is no benefit in terms of cardiovascular health and mortality from ho-

mocysteine-lowering therapies in ESKD patients. The lack of benefit is consistent across various subgroups and in sensitivity analyses. Future research efforts in ESKD should focus on alternative therapies for the prevention of cardiovascular events.

ACKNOWLEDGEMENTS

We would like to thank the referees for their comments and feedback during the preparation of this review.

REFERENCES

References to studies included in this review

ASFAST 2004 *{published data only}*

McGrath B, Zoungas S, McNeil J, Branley P, Kerr P, ASFAST Investigators. The atherosclerosis and folic acid supplementation trial in CRF (ASFAST): rationale, design and baseline results [abstract no: 65]. *Nephrology* 2002;**7** (Suppl 3):A17. [CENTRAL: CN–00856590;]

McGrath B, Zoungas S, McNeil J, Kerr PG. The atherosclerosis and folic acid supplementation trial in CRF (ASFAST): rationale, design and baseline results [abstract]. *Journal of the American Society of Nephrology* 2001;**12** (Program & Abstracts):228A. [CENTRAL: CN–00446685;]

Polkinghorne K, Kerr PG, Muske C, McGrath BP, Zoungas S, The ASFAST Investigators. The effect of lowering homocysteine on haemodialysis vascular access outcomes: the ASFAST randomised placebo controlled trial [abstract no: SU-FC110]. *Journal of the American Society of Nephrology* 2007;**18**(Abstracts):92A. [CENTRAL: CN–00716085;]

Zoungas S, Branley P, Kerr PG, Ristevski S, Muske C, Demos L, et al. Atherosclerosis and folic acid supplementation trial in chronic renal failure: baseline results. *Nephrology* 2004;**9**(3):130–41. [MEDLINE: 15189174]

Zoungas S, Cameron JD, Kerr PG, Wolfe R, Muske C, McNeil JJ, et al. Association of carotid intima-medial thickness and indices of arterial stiffness with cardiovascular disease outcomes in CKD. *American Journal of Kidney Diseases* 2007;**50**(4):622–30. [MEDLINE: 17900462]

Zoungas S, Kerr P, Lui M, Teede H, McNeil J, McGrath B, et al. Chronic kidney disease, cardiovascular events and the effect of diabetes: post hoc analyses from ASFAST [abstract no: 128]. *Nephrology* 2008;**13**(Suppl 3):A133.

Zoungas S, Lui M, Kerr PG, Teede HJ, McNeil JJ, McGrath BP, et al. Advanced chronic kidney disease, cardiovascular events and the effect of diabetes: data from the Atherosclerosis and Folic Acid Supplementation Trial. *Internal Medicine Journal* 2011;**41**(12):825–32. [MEDLINE: 20298505]

Zoungas S, McGrath BP, Branley P, Kerr PG, Muske C, Wolfe R, et al. Cardiovascular morbidity and mortality in the Atherosclerosis and Folic Acid Supplementation Trial (ASFAST) in chronic renal failure: a multicenter, randomized, controlled trial. *Journal of the American College of Cardiology* 2006;**47**(6):1108–16. [MEDLINE: 16545638]

Heinz 2009 *{published data only}*

Heinz J, Dierkes J, Domrose U, Neumann KH, Luley C. Influence of a supplementation with vitamins on morbidity and mortality of ESRD patients: a multi-center randomly designed double blinded intervention trial; Prismavit - prospective intervention study from Magdeburg with vitamins [abstract]. XIV Lipid Meeting; 2003 Dec 5-7; Leipzig, Germany. 2003:89. [CENTRAL: CN–00740532;]

Heinz J, Domrose U, Luley C, Westphal S, Kropf S, Neumann KH, et al. Influence of a supplementation with vitamins on cardiovascular morbidity and mortality in patients with end-stage renal disease: design and baseline data of a randomized clinical trial. *Clinical Nephrology* 2009;**71**(3):363–5. [MEDLINE: 19281755]

Heinz J, Kropf S, Domrose U, Westphal S, Borucki K, Luley C, et al. B vitamins and the risk of total mortality and cardiovascular disease in end-stage renal disease: results of a randomized controlled trial. *Circulation* 2010;**121**(12): 1432–8. [MEDLINE: 20231532]

HOST Study 2004 *{published data only}*

Brady CB, Gaziano JM, Cxypoliski RA, Guarino PD, Kaufman JS, Warren SR, et al. Homocysteine lowering and cognition in CKD: the Veterans Affairs homocysteine study. *American Journal of Kidney Diseases* 2009;**54**(3):440–9. [MEDLINE: 19628319]

Jamison R, Hartigan P, Gaziano M, Kaufman J, Goldfarb DS, Warren S, et al. High plasma homocysteine (Hcy) and cardiovascular (CV) disease in end stage (ESRD) and advanced chronic (ACKD) kidney disease. The VA Coop. study program homocysteine study (HOST) progress report [abstract no: PUB272]. *Journal of the American*

Society of Nephrology 2003;**14**(Nov):832A. [CENTRAL: CN–00550589;]
Jamison RL, Hartigan P, Gaziano JM, Fortmann SP, Goldfarb DS, Haroldson JA, et al. Design and statistical issues in the homocysteinemia in kidney and end stage renal disease (HOST) study. *Clinical Trials* 2004;**1**(5):451–60. [MEDLINE: 16279283]
Jamison RL, Hartigan P, Gaziano M, Kaufman J, Goldfarb DS, Warren S, et al. Cardiovascular disease in patients with advanced chronic kidney disease (ACKD) and hyperhomocysteinemia. The VA Coop. Studies Program Homocysteine Study (HOST) [abstract no: F-PO300]. *Journal of the American Society of Nephrology* 2004;**15**(Oct): 132A. [CENTRAL: CN–00550590;]
Jamison RL, Hartigan P, Kaufman JS, Goldfarb DS, Warren SR, Guarino P, et al. Homocysteine lowering effect on mortality and vascular disease in advanced chronic kidney disease and end stage renal disease [abstract no: M-FC-041]. 4th World Congress of Nephrology.19th International Congress of the International Society of Nephrology (ISN); 2007 Apr 21-25; Rio de Janeiro, Brazil. 2007:211.
Jamison RL, Hartigan P, Kaufman JS, Goldfarb DS, Warren SR, Guarino PD, et al. Effect of homocysteine lowering on mortality and vascular disease in advanced chronic kidney disease and end-stage renal disease: a randomized controlled trial.[Erratum appears in JAMA. 2008 Jul 9;300(2):170]. *JAMA* 2007;**298**(10):1163–70. [MEDLINE: 17848650]
Jamison RL, Shih MC, Humphries DE, Guarino PD, Kaufman JS, Goldfarb DS, et al. Effect of the MTHFR C677T and A1298C polymorphisms on survival in patients with advanced CKD and ESRD: a prospective study. *American Journal of Kidney Diseases* 2009;**53**(5):779–89. [MEDLINE: 19272686]
Jovanovich A, Chonchol M, Cheung AK, Kaufman JS, Greene T, Roberts WL, et al. Racial differences in markers of mineral metabolism in advanced chronic kidney disease. *Clinical Journal of the American Society of Nephrology: CJASN* 2012;**7**(4):640–7. [MEDLINE: 22383748]
Kendrick J, Cheung AK, Kaufman JS, Greene T, Roberts WL, Smits G, et al. Associations of plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D concentrations with death and progression to maintenance dialysis in patients with advanced kidney disease. *American Journal of Kidney Diseases* 2012;**60**(4):567–75. [MEDLINE: 22621970]
Kendrick JB, Cheung AK, Kaufman JS, Greene T, Roberts W, Smits G, et al. Fibroblast growth factor-23 and progression to dialysis in patients with advanced kidney disease [abstract no: F-PO1879]. *Journal of the American Society of Nephrology* 2009;**20**:542A. [CENTRAL: CN–00740513;]
Kendrick JB, Cheung AK, Kaufman JS, Greene T, Roberts W, Smits G, et al. Fibroblast growth factor-23 and the risk of death and cardiovascular events among patients with chronic kidney disease [abstract no: F-PO1873]. *Journal of the American Society of Nephrology* 2009;**20**:540A. [CENTRAL: CN–00740525;]
Kendrick JB, Cheung AK, Kaufman JS, Greene T, Roberts W, Smits G, et al. Higher intact parathyroid hormone levels are not associated with all-cause mortality or cardiovascular events in patients with advanced kidney disease [abstract no: F-PO1902]. *Journal of the American Society of Nephrology* 2009;**20**:547A. [CENTRAL: CN–00740514;]
Kendrick JB, Cheung AK, Kaufman JS, Greene T, Roberts W, Smits G, et al. Low serum levels of 1, 25-dihydroxyvitamin D, not 25-hydroxyvitamin D, is associated with all-cause mortality in chronic kidney disease [abstract no: TH-PO656]. *Journal of the American Society of Nephrology* 2009;**20**:265A. [CENTRAL: CN–00740559;]
Kendrick JB, Cheung AK, Kaufman JS, Greene T, Roberts W, Smits G, et al. Low serum levels of 1, 25-dihydroxyvitamin D, not 25-hydroxyvitamin D, is associated with progression to dialysis in patients with advanced kidney disease [abstract no: TH-PO647]. *Journal of the American Society of Nephrology* 2009;**20**:263A. [CENTRAL: CN–00740517;]
Montford JR, Chonchol M, Cheung AK, Kaufman JS, Greene T, Roberts WL, et al. Low body mass index and dyslipidemia in dialysis patients linked to elevated plasma fibroblast growth factor 23. *American Journal of Nephrology* 2013;**37**(3):183–90. [MEDLINE: 23428834]
Rafeq Z, Roh JD, Guarino P, Kaufman J, Joseph J. Adverse myocardial effects of B-vitamin therapy in subjects with chronic kidney disease and hyperhomocysteinaemia. *Nutrition Metabolism & Cardiovascular Diseases* 2013 Sep; **23**(9):836–42. [MEDLINE: 22902185]

Righetti 2003 ***{published data only}***

Righetti M. Homocysteine-lowering vitamin B treatment decreases cardiovascular events in hemodialysis patients. *Clinical Chemistry & Laboratory Medicine* 2007;**45**(12): 1586–9. [MEDLINE: 17937606]
Righetti M, Ferrario GM, Milani S, Serbelloni P, La Rosa L, Uccellini M, et al. Effects of folic acid treatment on homocysteine levels and vascular disease in hemodialysis patients. *Medical Science Monitor* 2003;**9**(4):19–24. [MEDLINE: 12709680]
Righetti M, Ferrario GM, Milani S, Serbelloni P, La Rosa L, Uccellini M, et al. Long-term effects of oral folic acid therapy on homocysteinemia and vascular disease in haemodialysis patients [abstract no: T237]. *Nephrology Dialysis Transplantation* 2002;**17**(Suppl 1):255. [CENTRAL: CN–00509435;]
Righetti M, Serbelloni P, Milani S, Ferrario G. Homocysteine-lowering vitamin B treatment decreases cardiovascular events in hemodialysis patients. *Blood Purification* 2006;**24**(4):379–86. [MEDLINE: 16755160]

Vianna 2007 ***{published data only}***

Vianna AC, Mocelin AJ, Matsuo T, Morais-Filho D, Largura A, Delfino VA, et al. Uremic hyperhomocysteinemia: a randomized trial of folate treatment for the prevention of cardiovascular events. *Hemodialysis International* 2007;**11** (2):210–6. [MEDLINE: 17403173]

Wrone 2004 *{published data only}*

Wrone E, Hornberger J, Zehnder J, McCann L, Coplon N, Fortmann S. Randomized trial of folic acid for homocysteine reduction in end-stage renal disease [abstract]. *American Journal of Kidney Diseases* 2002;**39**(4):A34. [CENTRAL: CN–00403143;]

Wrone EM, Hornberger JM, Zehnder JL, McCann LM, Coplon NS, Fortmann SP. Randomized trial of folic acid for prevention of cardiovascular events in end-stage renal disease. *Journal of the American Society of Nephrology* 2004; **15**(2):420–6. [MEDLINE: 14747389]

References to studies excluded from this review

Ali 2003 *{published data only}*

Ali Z, Idham C, Effendi I. The effect of n-acetylcysteine on homocysteine level in chronic hemodialysis patients: randomized control trial [abstract]. *Nephrology* 2003;**8** (Suppl 3):A62. [CENTRAL: CN–00671778;]

Alvares Delfino 2007 *{published data only}*

Alvares Delfino V, de Andrade Vianna AC, Mocelin AJ, Barbosa DS, Mise RA, Matsuo T. Folic acid therapy reduces plasma homocysteine levels and improves plasma antioxidant capacity in hemodialysis patients. *Nutrition* 2007;**23**(3):242–7. [MEDLINE: 17321110]

Anderson 2006 *{published data only}*

Anderson TJ, Sun YH, Hubacek J, Hyndman ME, Verma S, Shewchuk L, et al. Effects of folinic acid on forearm blood flow in patients with end-stage renal disease. *Nephrology Dialysis Transplantation* 2006;**21**(7):1927–33. [MEDLINE: 16520350]

Ardalan 2003 *{published data only}*

Ardalan MR, Etemadi J, Mortazavi M, Majidi J. Hyperhomocysteinaemia therapy in haemodialysis patients with combination of Vitamin B6, B12 and folic acid [abstract no: W467]. *Nephrology Dialysis Transplantation* 2003;**18**(4):696. [CENTRAL: CN–00716091;]

Ardalan 2003a *{published data only}*

Ardalan MR, Mortazavi M, Etemadi J. Hyperhomocysteinemia and its therapy in renal transplant recipients with combination of: Vit B6, Vit B12 and folic acid [abstract]. *Nephrology Dialysis Transplantation* 2003;**18** (Suppl 4):509–10. [CENTRAL: CN–00444217;]

Armada 2003 *{published data only}*

Armada E, Perez C, Otero A, Esteban J, Camba M, Gayoso P, et al. Neither folic nor folinic acid normalize homocysteine levels in hemodialysis patients. *Clinical Nephrology* 2003;**60**(3):168–75. [MEDLINE: 14524579]

Arnadottir 2003 *{published data only}*

Arnadottir M, Hultberg B. The effect of vitamin B12 on total plasma homocysteine concentration in folate-replete hemodialysis patients. *Clinical Nephrology* 2003;**59**(3): 186–9. [MEDLINE: 12653261]

ATIC Study 2005 *{published data only}*

Nanayakkara PW, Kiefte-De Jong JC, Stehouwer CD, van Ittersum FJ, Olthof MR, Kok RM, et al. Association between global leukocyte DNA methylation, renal function, carotid intima-media thickness and plasma homocysteine in patients with stage 2-4 chronic kidney disease. *Nephrology Dialysis Transplantation* 2008;**23**(8):2586–92. [MEDLINE: 18287179]

Nanayakkara PW, Kiefte-de Jong JC, ter Wee PM, Stehouwer CD, van Ittersum FJ, Olthof MR, et al. Randomized placebo-controlled trial assessing a treatment strategy consisting of pravastatin, vitamin E, and homocysteine lowering on plasma asymmetric dimethylarginine concentration in mild to moderate CKD. *American Journal of Kidney Diseases* 2009;**53**(1):41–50. [MEDLINE: 18786751]

Nanayakkara PW, Teerlink T, Stehouwer CD, Allajar D, Spijkerman A, Schalkwijk C, et al. Plasma asymmetric dimethylarginine (ADMA) concentration is independently associated with carotid intima-media thickness and plasma soluble vascular cell adhesion molecule-1 (sVCAM-1) concentration in patients with mild-to-moderate renal failure. *Kidney International* 2005;**68**(5):2230–6. [MEDLINE: 16221223]

Nanayakkara PW, van Guldener C, ter Wee PM, Scheffer PG, van Ittersum FJ, Twisk JW, et al. Effect of a treatment strategy consisting of pravastatin, vitamin E, and homocysteine lowering on carotid intima-media thickness, endothelial function, and renal function in patients with mild to moderate chronic kidney disease: results from the Anti-Oxidant Therapy in Chronic Renal Insufficiency (ATIC) Study. *Archives of Internal Medicine* 2007;**167**(12): 1262–70. [MEDLINE: 17592099]

Nanayakkara PW, van Guldener C, van Ittersum F, Stehouwer CD, ter Wee PM. Effect of an oxidative-stress-reducing strategy on carotid intima-media thickness, endothelial function and renal function in patients with mild-to-moderate chronic kidney disease [abstract no: F-PO145]. *Journal of the American Society of Nephrology* 2006; **17**(Abstracts):367A. [CENTRAL: CN–00602094;]

Nanayakkara PW, van Ittersum FJ, Fouque D, Charrie A, Stehouwer CD, ter Wee PM. Plasma adiponectin is inversely associated with renal function in patients with Stage 3 and 4 chronic kidney disease [abstract no: F-PO146]. *Journal of the American Society of Nephrology* 2006;**17**(Abstracts): 367A. [CENTRAL: CN–00602093;]

Thijs A, Nanayakkara PW, ter Wee PM, Huijgens PC, van Guldener C, Stehouwer CD. Mild-to-moderate renal impairment is associated with platelet activation: a cross-sectional study. *Clinical Nephrology* 2008;**70**(4):325–31. [MEDLINE: 18826858]

Veringa SJ, Nanayakkara PW, van Ittersum FJ, Vegting IL, van Guldener C, Smulders YM, et al. Effect of a treatment strategy consisting of pravastatin, vitamin E, and homocysteine lowering on arterial compliance and distensibility in patients with mild-to-moderate chronic kidney disease. *Clinical Nephrology* 2012;**78**(4):263–72. [MEDLINE: 22981031]

Azadibakhsh 2007 *{published data only}*

Azadibakhsh N, Hosseini RS, Atabak S, Nateghiyan N, Golestan B, Rad AH. Efficacy of folate and vitamin B12

in lowering homocysteine concentrations in hemodialysis patients. *Saudi Journal of Kidney Diseases & Transplantation* 2009;**20**(5):779–88. [MEDLINE: 19736473]

Azadibakhsh N, Hosseini RS, Atabak S, Nateghiyan N, Golestan B, Rad AH. The effect of folate and vitamin B12 supplementation on homocysteine concentrations: a study in hemodialysis patients. *Tehran University Medical Journal* 2007;**65**(8):49–56. [CENTRAL: CN–00796293;]

Beavers 2008 ***{published data only}***

Beavers KM, Beavers DP, Bowden RG, Wilson RL, Gentile M. Effect of over-the-counter fish-oil administration on plasma Lp(a) levels in an end-stage renal disease population. *Journal of Renal Nutrition* 2009;**19**(6):443–9. [MEDLINE: 19748798]

Beavers KM, Beavers DP, Bowden RG, Wilson RL, Gentile M. Omega-3 fatty acid supplementation and total homocysteine levels in end-stage renal disease patients. *Nephrology* 2008;**13**(4):284–8. [MEDLINE: 18331436]

Bennett-Richards 2002 ***{published data only}***

Bennett-Richards K, Kattenhorn M, Donald A, Oakley G, Varghese Z, Rees L, et al. Does oral folic acid lower total homocysteine levels and improve endothelial function in children with chronic renal failure?. *Circulation* 2002;**105**(15):1810–5. [MEDLINE: 11956124]

Bennett-Richards K, Taylor M, Oakley G, Varghese Z, Deanfield J, Rees L. Does oral folic acid lower total homocystine levels and improve endothelial function in children with CRF? [abstract]. *Pediatric Nephrology* 2001; **16**(8):C167. [CENTRAL: CN–00444396;]

Bostom 1996 ***{published data only}***

Bostom AG, Shemin D, Lapane KL, Hume AL, Yoburn D, Nadeau MR, et al. High dose-B-vitamin treatment of hyperhomocysteinemia in dialysis patients. *Kidney International* 1996;**49**(1):147–52. [MEDLINE: 8770960]

Bostom 2000 ***{published data only}***

Bostom AG, Shemin D, Bagley P, Massy ZA, Zanabli A, Christopher K, et al. Controlled comparison of L-5-methyltetrahydrofolate versus folic acid for the treatment of hyperhomocysteinemia in hemodialysis patients.[Erratum appears in Circulation 2000 Aug 1;102(5):598]. *Circulation* 2000;**101**(24):2829–32. [MEDLINE: 10859289]

Bostom AG, Shemin D, Bagley P, Massy ZA, Zanabli A, Spiegel P, et al. Reduced folates are an expensive treatment for hyperhomocysteinemia in hemodialysis patients with no greater efficacy than folic acid: results of a controlled comparison study [abstract]. *Journal of the American Society of Nephrology* 2000;**11**(Sept):257A. [CENTRAL: CN–00550713;]

Bostom AG, Shemin D, Gohh RY, Beaulieu AJ, Bagley P, Massy ZA, et al. Treatment of hyperhomocysteinemia in hemodialysis patients and renal transplant recipients. *Kidney International - Supplement* 2001;**59**(Suppl 78): S246–52. [MEDLINE: 11169020]

Bostom AG, Shemin D, Gohh RY, Beaulieu AJ, Jacques PF, Dworkin L, et al. Treatment of mild hyperhomocysteinemia in renal transplant recipients versus hemodialysis patients. *Transplantation* 2000;**69**(10):2128–31. [MEDLINE: 10852611]

Branley 2000 ***{published data only}***

Branley P, D'Intini V, Thomson N, Fraenkel M, McNeil JJ. Randomised placebo controlled clinical trial of supplementary folic acid in CRF [abstract]. *Nephrology* 2000;**5**(3):A79. [CENTRAL: CN–00400364;]

Brensing 2002 ***{published data only}***

Brensing KA, Kaschell D, Hages M, Lutjohann D, Sigit J, Pietrizik K, et al. Improved hyperhomocysteinemia in hemodialysed ESRD-patients by intravenous folate or folinic acid: a randomized controlled trial [abstract no: O100]. *Nephrology Dialysis Transplantation* 2002;**17**(Suppl 1):30. [CENTRAL: CN–00509104;]

Brensing 2003 ***{published data only}***

Brensing KA, Hages M, Raab P, Pietrzik K, von Bergmann K, Frotscher U, et al. Vitamin B12 and folic-acid as intravenous high-dose vitamin therapy for hyperhomocysteinemia in hemodialysed ESRD-patients: data of a prospective randomized controlled study [abstract no: SU-PO1048]. *Journal of the American Society of Nephrology* 2003;**14**(Nov): 766A. [CENTRAL: CN–00644257;]

Chang 2007 ***{published data only}***

Chang TY, Chou KJ, Tseng CF, Chung HM, Fang HC, Hung YM, et al. Effects of folic acid and vitamin B complex on serum C-reactive protein and albumin levels in stable hemodialysis patients. *Current Medical Research & Opinion* 2007;**23**(8):1879–86. [MEDLINE: 17605895]

Chiu 2009 ***{published data only}***

Chiu YW, Chang JM, Hwang SJ, Tsai JC, Chen HC. Pharmacological dose of vitamin B12 is as effective as low-dose folinic acid in correcting hyperhomocysteinemia of hemodialysis patients. *Renal Failure* 2009;**31**(4):278–83. [MEDLINE: 19462276]

Cianciolo 2008 ***{published data only}***

Cianciolo G, La Manna G, Coli L, Donati G, D'Addio F, Persici E, et al. 5-methyltetrahydrofolate administration is associated with prolonged survival and reduced inflammation in ESRD patients. *American Journal of Nephrology* 2008;**28**(6):941–8. [MEDLINE: 18587236]

Cutler 2009 ***{published data only}***

Cutler MJ, Urquhart BL, Freeman DJ, Spence JD, House AA. Mesna for the treatment of hyperhomocysteinemia in hemodialysis patients. *Blood Purification* 2009;**27**(3): 306–10. [MEDLINE: 19270449]

De Angelis 2007 ***{published data only}***

De Angelis S, Noce A, Dessi M, Pastore A, Scaccia F, Trombetta M, et al. Hyperhomocysteinemia and alternate vitamin supplementation [Iperomocisteinemia nei pazienti uremici: effetti della supplementazione alternata di acido folico e vitamina B 12]. *Giornale Italiano di Nefrologia* 2007;**24**(1):51–5. [MEDLINE: 17342693]

Dessi M, Di Giovamberardino G, Pieri M, Noce A, Zenobi R, Di Daniele N, et al. Influence of dialysis techniques and alternate vitamin supplementation on homocysteine levels in patients with known MTHFR genotypes. *Clinical &*

Experimental Nephrology 2015;**19**(1):140–5. [MEDLINE: 24652221]

Del Pozo 2005 *{published data only}*

Del Pozo C, Alvarez L, Lopez-Menchero R, Torregrosa I, Sanchez L, Albero MD. Optimization of a therapy schedule with folinic acid to treat hyperhomocysteinemia in patients on hemodialysis [abstract no: SP261]. *Nephrology Dialysis Transplantation* 2005;**20**(Suppl 5):v106. [CENTRAL: CN–00671828;]

De Vecchi 2001 *{published data only}*

De Vecchi AF, Patrosso C, Novembrino C, Finazzi S, Colucci P, De Franceschi M, et al. Folate supplementation in peritoneal dialysis patients with normal erythrocyte folate: effect on plasma homocysteine. *Nephron* 2001;**89**(3):297–302. [MEDLINE: 11598393]

De Vriese 2003 *{published data only}*

De Vriese AS, Langlois M, Bernard D, Geerolf I, Stevens L, Boelaert JR, et al. Effect of dialyser membrane pore size on plasma homocysteine levels in haemodialysis patients. *Nephrology Dialysis Transplantation* 2003;**18**(12):2596–600. [MEDLINE: 14605283]

Dierkes 1999 *{published data only}*

Dierkes J, Domrose U, Ambrosch A, Bosselmann HP, Neumann KH, Luley C. Response of hyperhomocysteinemia to folic acid supplementation in patients with end-stage renal disease. *Clinical Nephrology* 1999;**51**(2):108–15. [MEDLINE: 10069646]

Dierkes 2001 *{published data only}*

Dierkes J, Domrose U, Bosselmann KP, Neumann KH, Luley C. Homocysteine lowering effect of different multivitamin preparations in patients with end-stage renal disease. *Journal of Renal Nutrition* 2001;**11**(2):67–72. [MEDLINE: 11295026]

DIVINe Study 2010 *{published data only}*

House AA, Ehasziw M, Cattran DC, Churchill DN, Oliver MJ, Fine A, et al. Vitamin therapy for homocysteine accelerates loss of renal function in diabetic kidney disease [abstract no: SA-FC343]. *Journal of the American Society of Nephrology* 2009;**20**:80A. [CENTRAL: CN–00740523;]

House AA, Eliasziw M, Cattran DC, Churchill DN, Oliver MJ, Fine A, et al. Effect of B-vitamin therapy on progression of diabetic nephropathy: a randomized controlled trial. *JAMA* 2010;**303**(16):1603–9. [MEDLINE: 20424250]

Dobronravov 2008 *{published data only}*

Dobronravov V, Ardebili M, Golubev R, Galkina O, Nabokow A, Kliem V, et al. The effect of IV administration of sodium 2,3-dimercaptopropane-1-sulfonate (DMPS) and 8-week high-dosed IV vitamin B therapy on total plasma homocysteine (tHcy) in patients undergoing chronic hemodialysis (HD) [abstract no: PUB584]. *Journal of the American Society of Nephrology* 2008;**19**(Abstracts Issue):943A. [CENTRAL: CN–00758243;]

Ducloux 2002 *{published data only}*

Ducloux D, Aboubakr A, Motte G, Toubin G, Fournier V, Chalopin JM, et al. Hyperhomocysteinaemia therapy in haemodialysis patients: folinic versus folic acid in combination with vitamin B6 and B12. *Nephrology Dialysis Transplantation* 2002;**17**(5):865–70. [MEDLINE: 11981075]

Ducloux D, Aboubakr A, Motte G, Toubin G, Fournier V, Chalopin JM, et al. Hyperhomocysteinemia therapy in hemodialysis (HD) patients: folinic versus folic acid in combination with vitamin B6 and B12 [abstract]. *Journal of the American Society of Nephrology* 2001;**12**(Program & Abstracts):354A–5A. [CENTRAL: CN–00445156;]

Elian 2002 *{published data only}*

Elian KM, Hoffer LJ. Hydroxocobalamin reduces hyperhomocysteinemia in end-stage renal disease. *Metabolism: Clinical & Experimental* 2002;**51**(7):881–6. [MEDLINE: 12077735]

Friedman 2003 *{published data only}*

Friedman AN, Bostom AG, Laliberty P, Selhub J, Shemin D. The effect of N-acetylcysteine on plasma total homocysteine levels in hemodialysis: a randomized, controlled study. *American Journal of Kidney Diseases* 2003;**41**(2):442–6. [MEDLINE: 12552508]

Galli 2003 *{published data only}*

Galli F, Benedetti S, Buoncristiani U, Piroddi M, Conte C, Canestrari F, et al. The effect of PMMA-based protein-leaking dialyzers on plasma homocysteine levels. *Kidney International* 2003;**64**(2):748–55. [MEDLINE: 12846775]

Galli F, Benedetti S, Floridi A, Canestrari F, Piroddi M, Buoncristiani E, et al. Glycoxidation and inflammatory markers in patients on treatment with PMMA-based protein-leaking dialyzers. *Kidney International* 2005;**67**(2):750–9. [MEDLINE: 15673326]

Gonin 2003 *{published data only}*

Gonin JM, Nguyen H, Gonin R, Sarna A, Michels A, Masri-Imad F, et al. Controlled trials of very high dose folic acid, vitamins B12 and B6, intravenous folinic acid and serine for treatment of hyperhomocysteinemia in ESRD. *Journal of Nephrology* 2003;**16**(4):522–34. [MEDLINE: 14696754]

Gonin JM, Sarna A, Loya A, Gonin R, Chassaing C, Wainer I, et al. A double-blind, controlled study of folate and vitamin therapy for hyperhomocysteinemia in hemodialysis [abstract]. *Journal of the American Society of Nephrology* 2000;**11**(Sept):269A. [CENTRAL: CN–00755224;]

Gonin 2003a *{published data only}*

Gonin J, Nguyen H, Michels A, Santos A, Gonin R, Cary D, et al. Evaluation of folinic acid and serine in hyperhomocysteinemia in ESRD: a prospective placebo-controlled randomized study [abstract]. *Journal of the American Society of Nephrology* 2001;**12**(Program & Abstracts):356A. [CENTRAL: CN–00445513;]

Gonin JM, Nguyen H, Gonin R, Sarna A, Michels A, Masri-Imad F, et al. Controlled trials of very high dose folic acid, vitamins B12 and B6, intravenous folinic acid and serine for treatment of hyperhomocysteinemia in ESRD. *Journal of Nephrology* 2003;**16**(4):522–34. [MEDLINE: 14696754]

Hauser 2001 *{published data only}*

Hagen W, Hauser A, Rehak PH, Buchmayer H, Fodinger M, Horl WH, et al. Comparison of intravenous folinic acid with intravenous folic acid for the treatment of hyperhomocysteinemia in hemodialysis patients. A randomized, double blinded trial [abstract]. *Journal of the American Society of Nephrology* 2000;**11**(Sept):148A. [CENTRAL: CN–00583332;]

Hagen W, Kletzmayr J, Fodinger M, Hauser AC, Horl WH, Sunder-Plassmann G. Effect of intravenous folic acid or folinic acid therapy on mean arterial pressure and pulse pressure in hemodialysis patients [abstract]. *Journal of the American Society of Nephrology* 2001;**12**(Program & Abstracts):483A. [CENTRAL: CN–00583333;]

Hauser AC, Hagen W, Rehak PH, Buchmayer H, Fodinger M, Papagiannopoulos M, et al. Efficacy of folinic versus folic acid for the correction of hyperhomocysteinemia in hemodialysis patients. *American Journal of Kidney Diseases* 2001;**37**(4):758–65. [MEDLINE: 11273876]

Henning 2001 *{published data only}*

Henning BF, Zidek W, Riezler R, Graefe U, Tepel M. Homocyst(e)ine metabolism in hemodialysis patients treated with vitamins B6, B12 and folate. *Research in Experimental Medicine* 2001;**200**(3):155–68. [MEDLINE: 11426667]

Hoffer 2005 *{published data only}*

Hoffer LJ, Saboohi F, Golden M, Barre PE. Cobalamin dose regimen for maximum homocysteine reduction in end-stage renal disease. *Metabolism: Clinical & Experimental* 2005;**54**(6):835–40. [MEDLINE: 15931623]

Hoffer 2005a *{published data only}*

Hoffer LJ, Djahangirian O, Bourgouin PE, Eid J, Saboohi F. Comparative effects of hydroxocobalamin and cyanocobalamin on plasma homocysteine concentrations in end-stage renal disease. *Metabolism: Clinical & Experimental* 2005;**54**(10):1362–7. [MEDLINE: 16154437]

HOPE-2 Study 2006 *{published data only}*

Lonn E, Held C, Arnold JM, Probstfield J, McQueen M, Micks M, et al. Rationale, design and baseline characteristics of a large, simple, randomized trial of combined folic acid and vitamins B6 and B12 in high-risk patients: the Heart Outcomes Prevention Evaluation (HOPE)-2 trial. *Canadian Journal of Cardiology* 2006;**22**(1):47–53. [MEDLINE: 16450017]

Lonn E, Yusuf S, Arnold MJ, Sheridan P, Pogue J, Micks M, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease.[erratum appears in N Engl J Med. 2006 Aug 17;355(7):746]. *New England Journal of Medicine* 2006;**354**(15):1567–77. [MEDLINE: 16531613]

Mann JF, Sheridan P, McQueen MJ, Held C, Arnold JM, Fodor G, et al. Homocysteine lowering with folic acid and B vitamins in people with chronic kidney disease--results of the renal Hope-2 study. *Nephrology Dialysis Transplantation* 2008;**23**(2):645–53. [MEDLINE: 18003666]

Ray JG, Kearon C, Yi Q, Sheridan P, Lonn E, Heart Outcomes Prevention Evaluation (HOPE-2). Homocysteine-lowering therapy and risk for venous thromboembolism: a randomized trial.[Summary for patients in Ann Intern Med. 2007 Jun 5;146(11):I22; PMID: 17470823]. *Annals of Internal Medicine* 2007;**146**(11):761–7. [MEDLINE: 17470822]

Righetti M. Hopeful for a second HOPE-2 post hoc analysis. *Nephrology Dialysis Transplantation* 2008;**23**(7):2428–9. [MEDLINE: 18403437]

Saposnik G, Ray JG, Sheridan P, McQueen M, Lonn E. Homocysteine-lowering therapy and stroke risk, severity, and disability: additional findings from the HOPE 2 trial. *Stroke* 2009;**40**(4):1365–72. [MEDLINE: 19228852]

Sawka AM, Ray JG, Yi Q, Josse RG, Lonn E. Randomized clinical trial of homocysteine level lowering therapy and fractures. *Archives of Internal Medicine* 2007;**167**(19):2136–9. [MEDLINE: 17954810]

House 1999 *{published data only}*

House A, Freeman D. Larger intradialytic effect of high flux vs low flux polysulfone on homocysteine levels, but not on lipids or apo AI/CIII ratio [abstract]. *Journal of the American Society of Nephrology* 2001;**12**(Program & Abstracts):209A. [CENTRAL: CN–00445778;]

House AA, Donnelly JG. Effect of multivitamins on plasma homocysteine and folate levels in patients on hemodialysis. *ASAIO Journal* 1999;**45**(1):94–7. [MEDLINE: 9952016]

House AA, Donnelly JG. Impact of methylenetetrahydrofolate reductase (MTHFR) genotype on folate status and homocysteine (hcy) in hemodialysis patients [abstract]. *Journal of the American Society of Nephrology* 1999;**10**(Program & Abstracts):168A. [CENTRAL: CN–00756935;]

House AA, Wells GA, Donnelly JG, Nadler SP, Hebert PC. Effect of high flux vs low flux hemodialysis on homocysteine, lipoprotein(a) and lipid profiles: a prospective randomized trial [abstract]. *Journal of the American Society of Nephrology* 1998;**9**(Program & Abstracts):211A. [CENTRAL: CN–00401331;]

House AA, Wells GA, Donnelly JG, Nadler SP, Hebert PC. Randomized trial of high-flux vs low-flux haemodialysis: effects on homocysteine and lipids. *Nephrology Dialysis Transplantation* 2000;**15**(7):1029–34. [MEDLINE: 10862642]

House 2004 *{published data only}*

House AA, Eliasziw M, Urquhart BL, Freeman DJ, Spence JD. Dimercaptosuccinic acid for the treatment of hyperhomocysteinemia in hemodialysis patients: a placebo-controlled, double-blind, randomized trial. *American Journal of Kidney Diseases* 2004;**44**(4):689–94. [MEDLINE: 15384020]

Imani 2009 *{published data only}*

Imani H, Tabibi H, Atabak S, Rahmani L, Ahmadinejad M, Hedayati M. Effects of soy consumption on oxidative stress, blood homocysteine, coagulation factors, and phosphorus in peritoneal dialysis patients. *Journal of Renal Nutrition* 2009;**19**(5):389–95. [MEDLINE: 19577483]

Tabibi H, Imani H, Hedayati M, Atabak S, Rahmani L. Effects of soy consumption on serum lipids and apoproteins in peritoneal dialysis patients: a randomized controlled

trial. *Peritoneal Dialysis International* 2010;**30**(6):611–8. [MEDLINE: 20378840]

Isbel 2003 ***{published data only}***

Isbel NM, Reiger K, Hayley CM, Campbell SB, Burke J, Bofinger A, et al. Vitamin B12 is effective in the treatment of hyperhomocysteinaemia in patients with ESRD [abstract no: 58]. *Nephrology* 2003;**8**(Suppl 3):A69. [CENTRAL: CN–00758625;]

ISRCTN22151635 ***{published data only}***

ISRCTN22151635. Assessment of the lipid lowering agents on plasma homocysteine concentration and renal function. controlled-trials.com/ISRCTN22151635 (accessed 4 February 2016).

Jara 2001 ***{published data only}***

Jara A, Morales M. Intravenous folinic acid versus oral folic acid for the treatment of hyperhomocysteinemia in hemodialysis patients [abstract]. *Journal of the American Society of Nephrology* 2001;**12**(Program & Abstracts):357A. [CENTRAL: CN–00445900;]

Kazory 2008 ***{published data only}***

Kazory A, Kribs M, Fournier V, Motte G, Guy C, Devillard N, et al. Homocysteine lowering effect of adsorptive dialysis membranes: a multicenter, randomized, open study [abstract no: 118]. *American Journal of Kidney Diseases* 2008;**51**(4):A57. [CENTRAL: CN–00756882;]

Klemm 2004 ***{published data only}***

Klemm A, Franke C, Busch M, Muller A, Franke S, Lang D, et al. Influence of hemodialysis membrane permeability on serum levels of advanced glycation end products (AGEs) and homocysteine metabolites. *Clinical Nephrology* 2004; **61**(3):191–7. [MEDLINE: 15077870]

Kooshki 2011 ***{published data only}***

Kooshki A, Taleban FA, Tabibi H, Hedayati M. Effects of marine omega-3 fatty acids on serum systemic and vascular inflammation markers and oxidative stress in hemodialysis patients. *Annals of Nutrition & Metabolism* 2011;**58**(3): 197–202. [MEDLINE: 21757893]

Kooshki A, Taleban FA, Tabibi H, Hedayati M. Effects of omega-3 fatty acids on serum lipids, lipoprotein (a), and hematologic factors in hemodialysis patients. *Renal Failure* 2011;**33**(9):892–8. [MEDLINE: 21859401]

Koyama 2002 ***{published data only}***

Koyama K, Usami T, Takeuchi O, Morozumi K, Kimura G. Efficacy of methylcobalamin on lowering total homocysteine plasma concentrations in haemodialysis patients receiving high-dose folic acid supplementation. *Nephrology Dialysis Transplantation* 2002;**17**(5):916–22. [MEDLINE: 11981084]

Koyama 2010 ***{published data only}***

Koyama K, Ito A, Ichikawa T, Miura T, Ono M. Short term regimen of homocysteine-lowering therapy reduces serum concentration of asymmetric dimethylarginine in patients on chronic hemodialysis [abstract no: SaP317]. *Nephrology Dialysis Transplantation* 2007;**22**(Suppl 6): vi339. [CENTRAL: CN–00671829;]

Koyama K, Ito A, Yamamoto J, Nishio T, Ichikawa T. Co-administration of methylcobalamin and folic acid normalizes hyperhomocysteinemia and reduces arterial stiffness in hemodialsyis patients [abstract no: PUB074]. *Journal of the American Society of Nephrology* 2005;**16**:798A. [CENTRAL: CN–00676039;]

Koyama K, Ito A, Yamamoto J, Nishio T, Kajikuri J, Dohi Y, et al. Randomized controlled trial of the effect of short-term coadministration of methylcobalamin and folate on serum ADMA concentration in patients receiving long-term hemodialysis. *American Journal of Kidney Diseases* 2010;**55** (6):1069–78. [MEDLINE: 20430500]

Kuhlmann 2004 ***{published data only}***

Kuhlmann MK, Obeid R, Herrmann W. Normalization of plasma homocystein (Hcy) levels in hyperhomocysteinemic hemodialysis patients by intravenous dosage of vitamins B6, B12 and folic acid. [abstract no SA-PO345]. *Journal of the American Society of Nephrology* 2004;**15**(Oct):377A. [CENTRAL: CN–00757352;]

Kumar 2007b ***{published data only}***

Kumar R, Vincent L, Perkins NJ, Tobe SW. Impact of folic acid on homocysteine levels in haemodialysis patients, a randomized double blinded placebo controlled cross over trial [abstract no: SA-PO788]. *Journal of the American Society of Nephrology* 2007;**18**(Abstracts Issue):516A. [CENTRAL: CN–00716086;]

Kuo 2001a ***{published data only}***

Kuo HT, Tsai JC, Chen LN, Chen HC, Guh JY, Hwang SJ, et al. Intravenous methylcobalamin further improves hyperhomocysteinemia in hemodialysis patients under maintenance folic acid therapy: role of methyletetrahydrofolate reductase (mthfr) genotype [abstract]. *Nephrology Dialysis Transplantation* 2001;**16**(6): A87. [CN–00509297]

LANDMARK Study 2006 ***{published data only}***

Isbel N, Rakhit D, Armstrong K, Leano R, Hawley C, Campbell S, et al. Rapid progression of myocardial ischaemia in patients with chronic kidney disease is not altered by risk factor modification [abstract no: PS107]. *Nephrology* 2005;**10**(Suppl 3):A408. [CENTRAL: CN–00583922;]

Isbel NM, Haluska B, Johnson DW, Beller E, Hawley C, Marwick TH. Increased targeting of cardiovascular risk factors in patients with chronic kidney disease does not improve atheroma burden or cardiovascular function. *American Heart Journal* 2006;**151**(3):745–53. [MEDLINE: 16504645]

Isbel NM, Reiger K, Hawley CM, Campbell SB, Haluska B, Short L, et al. Aggressive intervention in traditional cardiovascular risk factors in patients with chronic renal failure does not improve atheroma burden, cardiovascular function or outcome [abstract]. *Nephrology* 2004;**9**(Suppl 1):A1–2. [CENTRAL: CN–00509247;]

Johnson DW, Armstrong K, Campbell SB, Mudge DW, Hawley CM, Coombes JS, et al. Metabolic

syndrome in severe chronic kidney disease: Prevalence, predictors, prognostic significance and effects of risk factor modification. *Nephrology* 2007;**12**(4):391–8. [MEDLINE: 17635756]

Rakhit DJ, Marwick TH, Armstrong KA, Johnson DW, Leano R, Isbel NM. Effect of aggressive risk factor modification on cardiac events and myocardial ischaemia in patients with chronic kidney disease. *Heart* 2006;**92**(10): 1402–8. [MEDLINE: 16606867]

Libetta 2004 ***{published data only}***

Libetta C, Corbetta R, Zucchi M, Gori E, Villa G, Bezoari G, et al. Treatment of hyperhomocysteinemia in hemodialysis patients reduce progressive atherosclerosis: a long-term controlled study [abstract no: SA-PO343]. *Journal of the American Society of Nephrology* 2004;**15**(Oct): 376A–7A. [CENTRAL: CN–00626028;]

Libetta C, Corbetta R, Zucchi M, Gori E, Villa G, Sepe V, et al. Long-term treatment of hyperhomocysteinemia prevents carotid artery atherosclerosis in haemodialysed patients [abstract]. 41st Congress. European Renal Association. European Dialysis and Transplantation Association; 2004 May 15-18; Lisbon, Portugal. 2004:4. [CENTRAL: CN–00604353;]

Libetta C, Villa G, Gori E, Zucchi M, Pisacco P, Bezoari G, et al. Vitamins supplementation effectiveness on hyperhomocysteinemia in hemodialyzed patients: a two-year single-blind randomized study [abstract no: SA-PO344]. *Journal of the American Society of Nephrology* 2004; **15**(Oct):377A. [CENTRAL: CN–00626027;]

Libetta C, Villa G, Gori E, Zucchi M, Sepe V, Pisacco P, et al. Effect of folate or folate plus vitamins B6 and B12 on hyperhomocysteinemia in hemodialyzed patients: a 2-year controlled randomized study [abstract]. 41st Congress. European Renal Association. European Dialysis and Transplantation Association; 2004 May 15-18; Lisbon, Portugal. 2004:126. [CENTRAL: CN–00636150;]

Madsen 2011 ***{published data only}***

Madsen T, Christensen JH, Toft E, Aardestrup I, Lundbye-Christensen S, Schmidt EB. Effect of intravenous omega-3 fatty acid infusion and hemodialysis on fatty acid composition of free fatty acids and phospholipids in patients with end-stage renal disease. *Jpen: Journal of Parenteral & Enteral Nutrition* 2011;**35**(1):97–106. [MEDLINE: 21224436]

Manns 2001 ***{published data only}***

Hyndman ME, Manns BJ, Snyder FF, Bridge PJ, Scott-Douglas NW, Fung E, et al. Vitamin B12 decreases, but does not normalize, homocysteine and methylmalonic acid in end-stage renal disease: a link with glycine metabolism and possible explanation of hyperhomocysteinemia in end-stage renal disease. *Metabolism: Clinical & Experimental* 2003;**52**(2):168–72. [MEDLINE: 12601627]

Manns B, Hyndman E, Burgess E, Parsons H, Schaefer J, Snyder F, et al. Oral vitamin B(12) and high-dose folic acid in hemodialysis patients with hyper-homocyst(e)inemia. *Kidney International* 2001;**59**(3):1103–9. [MEDLINE: 11231366]

Mazdeh 2005 ***{published data only}***

Abolghasemi R, Mazdeh MM, Khatami M, Lessan-Pezeshki M, Ahmadi F, Seifi S, et al. Hyperhomocysteinemia therapy in haemodialysis patients: folinic versus folic acid in combination with vitamin B6 and B12 [abstract no: MP318]. *Nephrology Dialysis Transplantation* 2005;**20** (Suppl 5):v307.

Mazdeh MM, Abolghasemi R, Khatami M, Lessan-Pezeshki M, Ahmadi F, Seifi S, et al. Hyperhomocysteinemia therapy in hemodialysis patients: folinic versus folic acid in combination with vitamin B6 and B12 [abstract no: W-PO40014]. *Nephrology* 2005;**10**(Suppl 1):A283. [CENTRAL: CN–00756890;]

McGregor 2000a ***{published data only}***

McGregor D, Shand B, Lynn K. A controlled trial of the effect of folate supplements on homocysteine, lipids and hemorheology in end-stage renal disease. *Nephron* 2000;**85** (3):215–20. [MEDLINE: 10867536]

Mudge 2005 ***{published data only}***

Mudge D, Rogers R, Hollett P, Law B, Reiger K, Petrie JJP, et al. Plasma homocysteine levels with standard high flux haemodialysis compared with FX class dialysers [abstract]. *Nephrology* 2004;**9**(Suppl 1):A16. [CENTRAL: CN–00509369;]

Mudge DW, Rogers R, Hollett P, Law B, Reiger K, Petrie JJ, et al. Randomized trial of FX high flux vs standard high flux dialysis for homocysteine clearance. *Nephrology Dialysis Transplantation* 2005;**20**(10):2178–85. [MEDLINE: 16030045]

Mueller 2001 ***{published data only}***

Mueller T, Mueller N, Moser R, Stief T, Celle D, Pietrizk K. Reduced folates have an anti-inflammatory effect in hemodialysis patients [abstract]. *Nephrology Dialysis Transplantation* 2003;**18**(Suppl 4):700. [CENTRAL: CN–00446856;]

Mueller TF, Mueller N, Moser R, Stief T, Nau H, Lange H, et al. Effect of folate therapy on the inflammatory burden in hemodialysis patients [abstract no: SA-FC185]. *Journal of the American Society of Nephrology* 2002;**13**(September, Program & Abstracts):38A. [CENTRAL: CN–00446855;]

Mueller TF, Mueller N, Moser R, Stief T, Ziegler A, Nau H, et al. Effect of oral substitution of reduced folates on homocysteine, neopterin, and lipid levels in patients treated with hemodialysis [abstract]. *Journal of the American Society of Nephrology* 2001;**12**(Program & Abstracts):360A–1A. [CENTRAL: CN–00756385;]

Muller 2001 ***{published data only}***

Muller A, Busch M, Stein G, Hein GE, Funfstuck R. L-methionine loading test for the prediction of increased total homocysteine levels due to long term l-methionine treatment [abstract]. *Journal of the American Society of Nephrology* 2001;**12**(Program & Abstracts):734A. [CENTRAL: CN–00757145;]

Nakamura 2003 ***{published data only}***

Nakamura T, Hirayama H, Tajiri M, Saionji K, Hata A. Methylenetetrahydrofolate reductase (MTHFR) gene polymorphism influences the efficacy of folic acid (FA)

and vitamin B12 (B12) on hyperhomocyteinemia in hemodialysis (HD) patients [abstract]. *Nephrology Dialysis Transplantation* 2003;**18**(Suppl 4):699–700. [CENTRAL: CN–00446896;]

Nakhoul 2004 ***{published data only}***

Nakhoul F, Abassi Z, Plawner M, Khankin E, Ramadan R, Lanir N, et al. Comparative study of response to treatment with supraphysiologic doses of B-vitamins in hyperhomocysteinemic hemodialysis patients. *Israel Medical Association Journal - Imaj* 2004;**6**(4):213–7. [MEDLINE: 15115259]

Plawner M, Nakhoul F, Khankin E, Laneer N, Brenner B, Green J. Folic acid and varying doses of B-vitamines in the treatment of hyperhomocystinemia in hemodialysis patients [abstract]. *Journal of the American Society of Nephrology* 2000;**11**(Sept):295A. [CENTRAL: CN–00644331;]

Nascimento 2010 ***{published data only}***

Nascimento MM, Suliman ME, Anderstam B, Silva MM, Hayashi S, Pecoits-Filho R, et al. Effect of N-acetylcysteine supplementation on inflammatory and oxidative stress markers in peritoneal dialysis patients: a randomized placebo controlled study [abstract no: F-PO769]. *Journal of the American Society of Nephrology* 2007;**18**(Abstracts): 270A. [CENTRAL: CN–00756376;]

Nascimento MM, Suliman ME, Silva M, Chinaglia T, Marchioro J, Hayashi SY, et al. Effect of oral N-acetylcysteine treatment on plasma inflammatory and oxidative stress markers in peritoneal dialysis patients: a placebo-controlled study. *Peritoneal Dialysis International* 2010;**30**(3):336–42. [MEDLINE: 20190028]

OPACH Study 2006 ***{published data only}***

Harving F, Svensson M, Flyvbjerg A, Schmidt EB, Jorgensen KA, Eriksen HH, et al. n-3 polyunsaturated fatty acids and adiponectin in patients with end-stage renal disease. *Clinical Nephrology* 2015;**83**(5):279–85. [MEDLINE: 25816805]

Kirkegaard E, Svensson M, Strandhave C, Schmidt EB, Jorgensen KA, Christensen JH. Marine n-3 fatty acids, atrial fibrillation and QT interval in haemodialysis patients. *British Journal of Nutrition* 2012;**107**(6):903–9. [MEDLINE: 21791142]

Rasmussen LE, Svensson M, Jorgensen KA, Schmidt EB, Christensen JH. The content of docosahexaenoic acid in serum phospholipid is inversely correlated with plasma homocysteine levels in patients with end-stage renal disease. *Nutrition Research* 2010;**30**(8):535–40. [MEDLINE: 20851307]

Svensson M, Christensen JH, Jorgensen KA, Schmidt EB. Omacor as secondary prevention against cardiovascular disease in patients undergoing chronic hemodialysis: a randomised, placebo controlled intervention study [abstract no: F-PO606]. *Journal of the American Society of Nephrology* 2005;**16**:466A. [CENTRAL: CN–00583663;]

Svensson M, Frobert O, Schmidt EB, Jorgensen KA, Simonsen U, Christensen JH. The effect of n-3 fatty acids on levels of methylarginines in patients with end-stage renal disease. *Journal of Nephrology* 2010;**23**(4):459–64. [MEDLINE: 20349405]

Svensson M, Schmidt EB, Jorgensen KA, Christensen JH. The effect of n-3 fatty acids on heart rate variability in patients treated with chronic hemodialysis. *Journal of Renal Nutrition* 2007;**17**(4):243–9. [MEDLINE: 17586422]

Svensson M, Schmidt EB, Jorgensen KA, Christensen JH. The effect of n-3 fatty acids on lipids and lipoproteins in patients treated with chronic haemodialysis: a randomized placebo-controlled intervention study. *Nephrology Dialysis Transplantation* 2008;**23**(9):2918–24. [MEDLINE: 18436564]

Svensson M, Schmidt EB, Jorgensen KA, Christensen JH, OPACH Study Group. N-3 fatty acids as secondary prevention against cardiovascular events in patients who undergo chronic hemodialysis: A randomized, placebo-controlled intervention trial. *Clinical Journal of the American Society of Nephrology: CJASN* 2006;**1**(4):780–6. [MEDLINE: 17699287]

Ossareh 2009 ***{published data only}***

Ossareh S, Shayan-Moghaddam H, Salimi A, Asgari M, Farrokhi F. Different doses of oral folic acid for homocysteine-lowering therapy in patients on hemodialysis: a randomized controlled trial.[Erratum appears in Iran J Kidney Dis. 2010 Jan;4(1):88 Note: Salimi, Ashraf [added]; Asgari, Mojgan [added]]. *Iranian Journal of Kidney Diseases* 2009;**3**(4):227–33. [MEDLINE: 19841527]

Pakfetrat 2013 ***{published data only}***

Pakfetrat M, Shahroodi JR, Zolgadr AA, Larie HA, Nikoo MH, Malekmakan L. Effects of zinc supplement on plasma homocysteine level in end-stage renal disease patients: a double-blind randomized clinical trial. *Biological Trace Element Research* 2013;**153**(1-3):11–5. [MEDLINE: 23475369]

Pastore 2006 ***{published data only}***

Pastore A, De Angelis S, Casciani S, Ruggia R, Di Giovamberardino G, Noce A, et al. Effects of folic acid before and after vitamin B12 on plasma homocysteine concentrations in hemodialysis patients with known MTHFR genotypes. *Clinical Chemistry* 2006;**52**(1):145–8. [MEDLINE: 16391331]

Peng 2005 ***{published data only}***

Peng L, Liu Q. A prospective, randomized, placebo-controlled study to evaluate the effect of combined treatment of folic acid and intravenous B-complex vitamins on hyperhomocysteinemia in hemodialysis patients [abstract no: W-PO40032]. *Nephrology* 2005;**10**(Suppl 1):A288. [CENTRAL: CN–00671827;]

Polkinghorne 2003 ***{published data only}***

Polkinghorne KR, Zoungas S, Branley P, Villanueva E, McNeil JJ, Atkins RC, et al. A randomised placebo controlled trial of intramuscular vitamin B12 (hydroxyocobalamin) for the treatment of hyperhomocysteinemia in haemodialysis patients [abstract]. Kongres Nasional VIII Annual Meeting Perhimpunan

Nefrologi Indonesia; 2002 Oct; Surabaya, Indonesia. 2002: 2.5. [CENTRAL: CN–00447252;]

Polkinghorne KR, Zoungas S, Branley P, Villanueva E, McNeil JJ, Atkins RC, et al. A randomized placebo controlled trial of intramuscular vitamin B12 (hydroxyocobalamin) for the treatment of hyperhomocysteinemia in haemodialysis patients [abstract no: SU-FC267]. *Journal of the American Society of Nephrology* 2002;**13**(September, Program & Abstracts):55A. [CENTRAL: CN–00447251;]

Polkinghorne KR, Zoungas S, Branley P, Villanueva E, McNeil JJ, Atkins RC, et al. Randomized, placebo-controlled trial of intramuscular vitamin B12 for the treatment of hyperhomocysteinaemia in dialysis patients. *Internal Medicine Journal* 2003;**33**(11):489–94. [MEDLINE: 14656250]

Polkinghorne KR, Zoungas S, Branley P, Villnueva E, McNeil J, Atkins RC, et al. A randomised placebo controlled trial of intramuscular vitamin B12 (hydroxyocobalamin) for the treatment of hyperhomocysteinemia in haemodialysis patients [abstract]. *Nephrology* 2002;**7**(Suppl 3):A68.

Poulia 2011 ***{published data only}***

Poulia KA, Panagiotakos DB, Tourlede E, Rezou A, Stamatiadis D, Boletis J, et al. Omega-3 fatty acids supplementation does not affect serum lipids in chronic hemodialysis patients. *Journal of Renal Nutrition* 2011;**21** (6):479–84. [MEDLINE: 21439849]

Sanchez Alvarez 2005 ***{published data only}***

Sanchez Alvarez JE, Perez Tamajon L, Hernandez D, Alvarez Gonzalez A, Delgado P, Lorenzo V. Efficacy and safety of two vitamin supplement regimens on homocysteine levels in hemodialysis patients. Prospective, randomized clinical trial. *Nefrologia* 2005;**25**(3):288–96. [MEDLINE: 16053010]

Sanchez JE, Molina E, De La Vega MJ, Hernandez D, Perez L, Garcia R, et al. Sustained effect of two vitamin supplement regimens on hyperhomocysteinemia in maintenance hemodialysis (MHD) patients [abstract no: F-PO773]. *Journal of the American Society of Nephrology* 2003; **14**(Nov):231A. [CENTRAL: CN–00583425;]

Scholze 2004 ***{published data only}***

Scholze A, Rinder C, Beige J, Riezler R, Zidek W, Tepel M. Acetylcysteine reduces plasma homocysteine concentration and improves pulse pressure and endothelial function in patients with end-stage renal failure. *Circulation* 2004;**109** (3):369–74. [MEDLINE: 14732754]

Scholze A, Rinder C, Beige J, Riezler R, Zidek W, Tepel M. Reduced plasma homocysteine concentration and improved pulse pressure in hemodialysis patients with acetylcysteine [abstract]. 41st Congress. European Renal Association. European Dialysis and Transplantation Association; 2004 May 15-18; Lisbon, Portugal. 2004:127. [CENTRAL: CN–00509467;]

Seo 2003 ***{published data only}***

Seo MD, Yoon S, Jeong JC, Choi SS, Kim SY, Son I, et al. Effects of folic acid treatment on homocysteine levels and echocardiographic findings in ESRD [abstract no: SA-PO900]. *Journal of the American Society of Nephrology* 2003; **14**(Nov):497A. [CN–00756462]

Sepe 1999 ***{published data only}***

Sepe V, Patrucco G, Santagostine A, Bolis V, Caminiti R, Cecere P, et al. Hyperhomocysteinemia [HHcy] is not associated with elevated platelet annexin V [plt a-v] expression in maintenance haemodialysis [HD] patients [abstract]. *Nephrology Dialysis Transplantation* 1999;**14**(9): A192. [CENTRAL: CN–00485810;]

Shemin 2001 ***{published data only}***

Shemin D, Bostom AG, Selhub J. Treatment of hyperhomocysteinemia in end-stage renal disease. *American Journal of Kidney Diseases* 2001;**38**(4 Suppl 1):S91–4. [MEDLINE: 11576930]

Signorelli 2006 ***{published data only}***

Signorelli SS, Fatuzzo P, Rapisarda F, Neri S, Ferrante M, Oliveri CG, et al. A randomised, controlled clinical trial evaluating changes in therapeutic efficacy and oxidative parameters after treatment with propionyl L-carnitine in patients with peripheral arterial disease requiring haemodialysis. *Drugs & Aging* 2006;**23**(3):263–70. [MEDLINE: 16608381]

Signorelli SS, Fatuzzo P, Rapisarda F, Neri S, Ferrante M, Oliveri CG, et al. Propionyl-L-carnitine therapy: effects on endothelin-1 and homocysteine levels in patients with peripheral arterial disease and end-stage renal disease. *Kidney & Blood Pressure Research* 2006;**29**(2):100–7. [MEDLINE: 16809937]

Skoutakis 1975 ***{published data only}***

Skoutakis VA, Acchiardo SR, Meyer MC, Hatch FE. Folic acid dosage for chronic hemodialysis patients. *Clinical Pharmacology & Therapeutics* 1975;**18**(2):200–4. [MEDLINE: 1098832]

Stavrianaki 2002 ***{published data only}***

Stavrianaki D, Bagiatoudi G, Salpigidis K, Sarris E, Siakotos M. Treatment efficacy of folic or folinic acid in lowering total plasma homocysteine levels in patients on hemodialysis [abstract]. *Nephrology Dialysis Transplantation* 2002;**17** (Suppl 12):256. [CENTRAL: CN–00758491;]

Tamadon 2011 ***{published data only}***

Tamadon MR, Jamshidi L, Soliemani A, Ghorbani R, Malek F, Malek M. Effect of different doses of folic acid on serum homocysteine level in patients on hemodialysis. *Iranian Journal of Kidney Diseases* 2011;**5**(2):93–6. [MEDLINE: 21368386]

Tayyebi-Khosroshahi 2010 ***{published data only}***

Tayyebi-Khosroshahi H, Houshyar J, Tabrizi A, Vatankhah AM, Razzagi ZN, Dehghan-Hesari R. Effect of omega-3 fatty acid on oxidative stress in patients on hemodialysis. *Iranian Journal of Kidney Diseases* 2010;**4**(4):322–6. [MEDLINE: 20852375]

Tepel 2003 ***{published data only}***

Tepel M, van der Giet M, Statz M, Jankowski J, Zidek W. The antioxidant acetylcysteine reduces cardiovascular events in patients with end-stage renal failure: a randomized,

controlled trial. *Circulation* 2003;**107**(7):992–5. [MEDLINE: 12600912]

Thaha 2006 ***{published data only}***

Thaha M, Widodo, Yogiantoro M, Tomino Y. Reduction of pulse pressure by intravenous N-acetylcyseine administration in chronic hemodialysis patients [abstract no: 1620]. *Nephrology* 2006;**11**(Suppl 2):A33. [CENTRAL: CN–00653775;]

Thaha M, Yogiantoro M, Tomino Y. Intravenous N-acetylcysteine during haemodialysis reduces the plasma concentration of homocysteine in patients with end-stage renal disease. *Clinical Drug Investigation* 2006;**26**(4): 195–202. [MEDLINE: 17163251]

Thaha M, Yogiantoro M, Tomino Y. Intravenous N-acetylcysteine during haemodialysis reduces the plasma concentration of homocysteine in patients with end-stage renal disease [abstract no: 1560]. *Nephrology* 2006;**11** (Suppl 2):A18.

Thaha 2008 ***{published data only}***

Thaha M, Widodo B, Pranawa M, Yogiantoro HM, Tomino Y. Intravenous N-acetylcysteine during hemodialysis reduces homocysteine and asymmetric dimethylarginine in ESRD patients: a randomized double blind controlled trial [abstract no: 1159]. *Nephrology* 2007;**12**(Suppl 2):A40. [CENTRAL: CN–00740521;]

Thaha M, Widodo, Pranawa W, Yogiantoro M, Tomino Y. Intravenous N-acetylcysteine during hemodialysis reduces asymmetric dimethylarginine level in end-stage renal disease patients. *Clinical Nephrology* 2008;**69**(1):24–32. [MEDLINE: 18226399]

Thaha 2009 ***{published data only}***

Thaha M, Mohani CI, Yogiantoro HM, Tomino Y. Oral n-acetyl cysteine to treat non-diabetic chronic kidney disease stage 1-4 with albuminuria [abstract no: SA-PO2242]. *Journal of the American Society of Nephrology* 2009;**20**:622A. [CENTRAL: CN–00740560;]

Thambyrajah 2000 ***{published data only}***

Thambyrajah J, Landray MJ, McGlynn FJ, Jones HJ, Wheeler DC, Townend JN. Does folic acid decrease plasma homocysteine and improve endothelial function in patients with predialysis renal failure?. *Circulation* 2000;**102**(8): 871–5. [MEDLINE: 10952955]

Thambyrajah J, Landray MJ, Townend JN, Wheeler DC. Folic acid decreases plasma homocysteine but does not improve endothelial function in chronic renal failure [abstract]. *Journal of the American Society of Nephrology* 2000;**11**(Sept):372A. [CENTRAL: CN–00583252;]

Tobe 1999 ***{published data only}***

Tobe SW, Helmers K, Naimark DMJ, Perkins N, Baker B. Impact on homocysteine levels of folic acid and adherance in haemodialysis patients. A randomized double blind placebo cross over trial [abstract no: A1332]. *Journal of the American Society of Nephrology* 2000;**11**(Sept):253A. [CENTRAL: CN–00583286;]

Tobe SW, Naimark DN, Helmers KF, Perkins NJ, Baker B. Plasma homocysteine (hcy) levels in patients on chronic haemodialysis are inversely correlated with folate and B12 levels [abstract]. *Journal of the American Society of Nephrology* 1999;**10**(Program & Abstracts):306A. [CENTRAL: CN–00583285;]

Tochihara 2008 ***{published data only}***

Tochihara Y, Whiting MJ, Barbara JA, Mangoni AA. Effects of pre- vs. intra-dialysis folic acid on arterial wave reflections and endothelial function in patients with end-stage renal disease. *British Journal of Clinical Pharmacology* 2008;**66** (5):717–22. [MEDLINE: 18754845]

Treleaven 2001 ***{published data only}***

Treleaven D, Gough J, Lonn E, Strickland D, Kitching A, Churchill D, et al. High dose folic acid in hemodialysis patients results in frequent side effects without improvement in plasma homocysteine levels [abstract]. *Journal of the American Society of Nephrology* 2001;**12**(Program & Abstracts):365A. [CENTRAL: CN–00583283;]

Tremblay 2000 ***{published data only}***

Tremblay R, Bonnardeaux A, Geadah D, Busque L, Lebrun M, Ouimet D, et al. Hyperhomocysteinemia in hemodialysis patients: effects of 12-month supplementation with hydrosoluble vitamins. *Kidney International* 2000;**58** (2):851–8. [MEDLINE: 10916110]

Trimarchi 2002 ***{published data only}***

Trimarchi H, Schiel A, Freixas E, Diaz M. Randomized trial of methylcobalamin and folate effects on homocysteine in hemodialysis patients. *Nephron* 2002;**91**(1):58–63. [MEDLINE: 12021520]

Tungkasereerak 2006 ***{published data only}***

Tungkasereerak P, Chaiyasoot W, Taruangsri P, Leowattana W, Vasuvattakul S, Vareesangthip K, et al. Can folate and vitamin B supplementation reduce total homocysteine levels and atherosclerosis in hemodialysis patients? [abstract no: SA-PO472]. *Journal of the American Society of Nephrology* 2004;**15**(Oct):406A. [CENTRAL: CN–00583721;]

Tungkasereerak P, Ong-ajyooth L, Chaiyasoot W, Ong-ajyooth S, Leowattana W, Vasuvattakul S, et al. Effect of short-term folate and vitamin B supplementation on blood homocysteine level and carotid artery wall thickness in chronic hemodialysis patients. *Journal of the Medical Association of Thailand* 2006;**89**(8):1187–93. [MEDLINE: 17048428]

Urquhart 2008 ***{published data only}***

Urquhart BL, Freeman DJ, Cutler MJ, Mainra R, Spence JD, House AA. Mesna for treatment of hyperhomocysteinemia in hemodialysis patients: a placebo-controlled, double-blind, randomized trial. *Clinical Journal of the American Society of Nephrology: CJASN* 2008;**3**(4): 1041–7. [MEDLINE: 18337551]

van Guldener 1998 ***{published data only}***

van Guldener C, Janssen M, Lambert J, ter Wee P, Donker A, Stehonwer C. Treatment of hyperhomocysteinaemia with folic acid does not ameliorate endothelial function in chronic haemodialysis patients [abstract]. *Nephrology*

Dialysis Transplantation 1997;**12**(9):A114. [CENTRAL: CN–00261358;]

van Guldener C, Janssen MJ, Lambert J, ter Wee PM, Donker AJ, Stehouwer CD. Folic acid treatment of hyperhomocysteinemia in peritoneal dialysis patients does not ameliorate endothelial function [abstract]. *Journal of the American Society of Nephrology* 1997;**8**(Program & Abstracts):274A. [CENTRAL: CN–00448137;]

van Guldener C, Janssen MJ, Lambert J, ter Wee PM, Donker AJ, Stehouwer CD. Folic acid treatment of hyperhomocysteinemia in peritoneal dialysis patients: no change in endothelial function after long-term therapy. *Peritoneal Dialysis International* 1998;**18**(3):282–9. [MEDLINE: 9663892]

van Guldener C, Janssen MJ, Lambert J, ter Wee PM, Jakobs C, Donker AJ, et al. No change in impaired endothelial function after long-term folic acid therapy of hyperhomocysteinaemia in haemodialysis patients. *Nephrology Dialysis Transplantation* 1998;**13**(1):106–12. [MEDLINE: 9481724]

van Guldener C, Janssen MJ, Stehouwer CD, Ter Wee PM, Donker AJ. Treatment of hyperhomocysteinemia in chronic dialysis patients with folic acid and betaine [abstract no: A1266]. *Journal of the American Society of Nephrology* 1996; **7**(9):1502. [CENTRAL: CN–00758506;]

van Guldener C, Janssen MJ, Stehouwer CD, ter Wee PM, Donker AJ. Folic acid and betaine in the treatment of hyperhomocysteinaemia in haemodialysis patients [abstract]. *Netherlands Journal of Medicine* 1996;**48**(5):A67. [CENTRAL: CN–00416837;]

van Guldener C, Janssen MJ, de Meer K, Donker AJ, Stehouwer CD. Effect of folic acid and betaine on fasting and postmethionine-loading plasma homocysteine and methionine levels in chronic haemodialysis patients. *Journal of Internal Medicine* 1999;**245**(2):175–83. [MEDLINE: 10081520]

van Guldener C, Lambert J, ter Wee PM, Donker AJ, Stehouwer CD. Carotid artery stiffness in patients with end-stage renal disease: no effect of long-term homocysteine-lowering therapy. *Clinical Nephrology* 2000;**53**(1):33–41. [MEDLINE: 10661480]

Van Tellingen 2001 ***{published data only}***

Van Tellingen A, Grooteman MP, Bartels PC, Van Limbeek J, Van Guldener C, Wee PM, et al. Long-term reduction of plasma homocysteine levels by super-flux dialyzers in hemodialysis patients. *Kidney International* 2001;**59**(1): 342–7. [MEDLINE: 11135089]

VIENNA Study 2000 ***{published data only}***

Sunder-Plassmann G, Fodinger M, Buchmayer H, Papagiannopoulos M, Wojcik J, Kletzmayr J, et al. Effect of high dose folic acid therapy on hyperhomocysteinemia in hemodialysis patients: results of the Vienna multicenter study. *Journal of the American Society of Nephrology* 2000;**11** (6):1106–16. [MEDLINE: 10820175]

Sunder-Plassmann G, Fodinger M, Buchmayer H, Wolfl G, Papagiannoupoulos M, Wojzik J, et al. High dose folic acid therapy in hemodialysis (HD) patients. The Vienna multicenter study [abstract]. *Journal of the American Society of Nephrology* 1999;**10**(Program & Abstracts):269A. [CENTRAL: CN–00756862;]

Vrentzos 2001 ***{published data only}***

Vrentzos G, Ganotakis E, Vardakis K, Maliaraki N, Stratigis S, Stilianou K, et al. Effect of vitamin B12 supplementation in serum total homocysteine and folate in patients with end-stage renal failure [abstract]. *Atherosclerosis Supplements* 2001;**2**(2):107. [CENTRAL: CN–00671820;]

Vychytil 2003 ***{published data only}***

Vychytil A, Fodinger M, Pleiner J, Mullner M, Konner P, Skoupy S, et al. Acute effect of amino acid peritoneal dialysis solution on vascular function. *American Journal of Clinical Nutrition* 2003;**78**(5):1039–45. [MEDLINE: 14594793]

Vychytil A, Fodinger M, Pleiner J, Mullner M, Wolzt M, Sunder-Plassmann G. Acute effect of amino acid peritoneal dialysis (PD) solution on vascular function - no association with HCY [abstract]. *Journal of Inherited Metabolic Disease* 2003;**26**(Suppl 1):94. [CENTRAL: CN–00677763;]

Vychytil A, Foedinger M, Pleiner J, Muellner M, Konner P, Skoupy S, et al. Acute effect of amino acid peritoneal dialysis solution on vascular function [abstract]. *Nephrology Dialysis Transplantation* 2003;**18**(Suppl 4):215.

Vychytil A, Foedinger M, Pleiner J, Muellner M, Konner P, Skoupy S, et al. Acute effect of amino acid peritoneal dialysis solution on vascular function. [abstract no: SU-PO935]. *Journal of the American Society of Nephrology* 2003; **14**(Nov):741A.

Westphal 2001 ***{published data only}***

Westphal S, Dierkes J, Luley C. Effects of fenofibrate and gemfibrozil on plasma homocysteine. *Lancet* 2001;**358** (9275):39–40. [MEDLINE: 11454380]

Yango 2001 ***{published data only}***

Ghandour H, Bagley PJ, Shemin D, Hsu N, Jacques PF, Dworkin L, et al. Distribution of plasma folate forms in hemodialysis patients receiving high daily doses of L-folinic or folic acid. *Kidney International* 2002;**62**(6):2246–9. [MEDLINE: 12427152]

Yango A, Shemin D, Hsu N, Jacques PF, Dworkin L, Selhub J, et al. Rapid communication: L-folinic acid versus folic acid for the treatment of hyperhomocysteinemia in hemodialysis patients. *Kidney International* 2001;**59**(1): 324–7. [MEDLINE: 11135086]

Zeman 2006 ***{published data only}***

Zeman M, Zak A, Vecka M, Tvrzicka E, Pisarikova A, Stankova B. N-3 fatty acid supplementation decreases plasma homocysteine in diabetic dyslipidemia treated with statin-fibrate combination. *Journal of Nutritional Biochemistry* 2006;**17**(6):379–84. [MEDLINE: 16214329]

Zuo 2001 ***{published data only}***

Zuo L, Wang M, Feng L, Wei H, Wang H. Can high dose of folic acid normalize fast total plama homocysteine (thcy) level in maintenance hemodialysis patients? [abstract]. *Journal of the American Society of Nephrology* 2001;**12**

(Program & Abstracts):421A. [CENTRAL: CN–00689429;]

References to studies awaiting assessment

NCT00004495 ***{published data only}***
Wilcox CS. Randomized study of folic acid therapy for hyperhomocysteinemia in patients with end stage renal disease receiving hemodialysis. clinicaltrials.gov/ct2/show/NCT00004495 (accessed 18 February 2014).

Soleimani 2011 ***{published data only}***
Soleimani A, Usefzadeh M, Mianehsaz E, Foroozanfard F, Nikoueinejad H, Moraveji SA, et al. Comparison of oral folic acid and folinic acid on blood homocysteine level of patients on hemodialysis. *Iranian Journal of Kidney Diseases* 2011;**5**(1):45–9. [MEDLINE: 21189434]

Tayebi-Khosroshahi 2013 ***{published data only}***
Tayebi-Khosroshahi H, Dehgan R, Habibi AB, Safaian A, Panahi F, Estakhri R, et al. Effect of omega-3 supplementation on serum level of homocysteine in hemodialysis patients. *Iranian Journal of Kidney Diseases* 2013;**7**(6):479–84. [MEDLINE: 24241095]

Additional references

Andreucci 2004
Andreucci VE, Fissell RB, Bragg-Gresham JL, Ethier J, Greenwood R, Pauly M, et al. Dialysis Outcomes and Practice Patterns Study (DOPPS) data on medications in hemodialysis patients. *American Journal of Kidney Diseases* 2004;**44**(5 Suppl 2):61–7. [MEDLINE: 15486876]

Aucella 2005
Aucella F, Margaglione M, Grandone E, Vigilante M, Gatta G, Forcella M, et al. The C677T methylenetetrahydrofolate reductase gene mutation does not influence cardiovascular risk in the dialysis population: results of a multicentre prospective study. *Nephrology Dialysis Transplantation* 2005; **20**(2):382–6. [MEDLINE: 15618240]

Baigent 2000
Baigent C, Burbury K, Wheeler D. Premature cardiovascular disease in chronic renal failure. *Lancet* 2000;**356**(9224): 147–52. [MEDLINE: 10963260]

Bostom 1999
Bostom AG, Culleton BF. Hyperhomocysteinemia in chronic renal disease. *Journal of the American Society of Nephrology* 1999;**10**(4):891–900. [MEDLINE: 10203375]

Chauveau 1993
Chauveau P, Chadefaux B, Coude M, Aupetit J, Hannedouche T, Kamoun P, et al. Hyperhomocysteinemia, a risk factor for atherosclerosis in chronic uremic patients. *Kidney International - Supplement* 1993;**41**:S72–7. [MEDLINE: 8320950]

de Jager 2009
de Jager DJ, Grootendorst DC, Jager KJ, van Dijk PC, Tomas LM, Ansell D, et al. Cardiovascular and noncardiovascular mortality among patients starting dialysis. *JAMA* 2009;**302**(16):1782–9. [MEDLINE: 19861670]

Ducloux 2006
Ducloux D, Klein A, Kazory A, Devillard N, Chalopin JM. Impact of malnutrition-inflammation on the association between homocysteine and mortality. *Kidney International* 2006;**69**(2):331–5. [MEDLINE: 16408123]

Egger 1997
Egger M, Davey-Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple graphical test. *BMJ* 1997;**315**(7109):629–34. [MEDLINE: 9310563]

Eikelboom 1999
Eikelboom JW, Lonn E, Genest J Jr, Hankey G, Yusuf S. Homocyst(e)ine and cardiovascular disease: a critical review of the epidemiologic evidence. *Annals of Internal Medicine* 1999;**131**(5):363–75. [MEDLINE: 10475890]

Foley 1998
Foley RN, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. *Journal of the American Society of Nephrology* 1998;**9**(12 Suppl):S16–23. [MEDLINE: 11443763]

Freidman 2001
Friedman AN, Bostom AG, Selhub J, Levey AS, Rosenberg IH. The kidney and homocysteine metabolism. *Journal of the American Society of Nephrology* 2001;**12**(10):2181–9. [MEDLINE: 11562419]

Go 2004
Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization.[Erratum appears in N Engl J Med. 2008;18(4):4]. *New England Journal of Medicine* 2004;**351**(13):1296–305. [MEDLINE: 15385656]

Gonin 2005
Gonin JM. Folic acid supplementation to prevent adverse events in individuals with chronic kidney disease and end stage renal disease. *Current Opinion in Nephrology & Hypertension* 2005;**14**(3):277–81. [MEDLINE: 15821423]

Haynes 2012
Haynes R, Clarke R. Homocysteine, the kidney, and vascular disease. *BMJ* 2012;**344**:e3925. [MEDLINE: 22695904]

Higgins 2003
Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327** (7414):557–60. [MEDLINE: 12958120]

Higgins 2011
Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

HSC 2002
Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. *JAMA* 2002;**288**(16):2015–22. [MEDLINE: 12387654]

Huang 2012
Huang T, Chen Y, Yang B, Yang J, Wahlqvist ML, Li D. Meta-analysis of B vitamin supplementation on plasma homocysteine, cardiovascular and all-cause mortality. *Clinical Nutrition* 2012;**31**(4):448–54. [MEDLINE: 22652362]

Jardine 2012
Jardine MJ, Kang A, Zoungas S, Navaneethan SD, Ninomiya T, Nigwekar SU, et al. The effect of folic acid based homocysteine lowering on cardiovascular events in people with kidney disease: systematic review and meta-analysis. *BMJ* 2012;**344**:e3533. [MEDLINE: 22695899]

K/DOQI 2005
K/DOQI Workgroup. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *American Journal of Kidney Diseases* 2005;**45**(4 Suppl 3):S1–153. [MEDLINE: 15806502]

Kalantar-Zadeh 2004
Kalantar-Zadeh K, Block G, Humphreys MH, McAllister CJ, Kopple JD. A low, rather than a high, total plasma homocysteine is an indicator of poor outcome in hemodialysis patients. *Journal of the American Society of Nephrology* 2004;**15**(2):442–53. [MEDLINE: 14747392]

Kalantar-Zadeh 2005
Kalantar-Zadeh K, Abbott KC, Salahudeen AK, Kilpatrick RD, Horwich TB. Survival advantages of obesity in dialysis patients. *American Journal of Clinical Nutrition* 2005;**81**(3): 543–54. [MEDLINE: 15755821]

Kanbay 2010
Kanbay M, Afsar B, Gusbeth-Tatomir P, Covic A. Arterial stiffness in dialysis patients: where are we now? . *International Urology & Nephrology* 2010;**42**(3):741–52. [MEDLINE: 19924558]

Klerk 2002
Klerk M, Verhoef P, Clarke R, Blom HJ, Kok FJ, Schouten EG, et al. MTHFR 677C-->T polymorphism and risk of coronary heart disease: a meta-analysis. *JAMA* 2002;**288** (16):2023–31. [MEDLINE: 12387655]

McDonald 2007
McDonald S, Excell L, Livingston B. ANZDATA Registry 2007 Report. Chapter 3 Deaths. www.anzdata.org.au/anzdata/AnzdataReport/30thReport/Ch03Deaths.pdf 2007; Vol. (accessed 19 January 2016).

Menon 2006
Menon V, Sarnak MJ, Greene T, Wang X, Pereira AA, Beck GJ, et al. Relationship between homocysteine and mortality in chronic kidney disease. *Circulation* 2006;**113** (12):1572–7. [MEDLINE: 16549639]

Moustapha 1998
Moustapha A, Naso A, Nahlawi M, Gupta A, Arheart KL, Jacobsen DW, et al. Prospective study of hyperhomocysteinemia as an adverse cardiovascular risk factor in end-stage renal disease.[Erratum appears in Circulation 1998 Feb 24;97(7):711]. *Circulation* 1998;**97** (2):138–41. [MEDLINE: 9445164]

Pan 2012
Pan Y, Guo LL, Cai LL, Zhu XJ, Shu JL, Liu XL, et al. Homocysteine-lowering therapy does not lead to reduction in cardiovascular outcomes in chronic kidney disease patients: a meta-analysis of randomised, controlled trials. *British Journal of Nutrition* 2012;**108**(3):400–7. [MEDLINE: 22244447]

Robinson 1996
Robinson K, Gupta A, Dennis V, Arheart K, Chaudhary D, Green R, et al. Hyperhomocysteinemia confers an independent increased risk of atherosclerosis in end-stage renal disease and is closely linked to plasma folate and pyridoxine concentrations. *Circulation* 1996;**94**(11): 2743–8. [MEDLINE: 8941098]

Suliman 2007
Suliman ME, Lindholm B, Bárány P, Qureshi AR, Stenvinkel P. Homocysteine-lowering is not a primary target for cardiovascular disease prevention in chronic kidney disease patients. *Seminars in Dialysis* 2007;**20**(6):523–9. [MEDLINE: 17991198]

USRDS 2007
U.S. Renal Data System, USRDS 2007 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2007. www.usrds.org/atlas07.aspx (accessed January 2016).

van Guldener 2006
van Guldener C. Why is homocysteine elevated in renal failure and what can be expected from homocysteine-lowering?. *Nephrology Dialysis Transplantation* 2006;**21**(5): 1161–6. [MEDLINE: 16490741]

VITATOPS 2010
VITATOPS Trial Study Group. B vitamins in patients with recent transient ischaemic attack or stroke in the VITAmins TO Prevent Stroke (VITATOPS) trial: a randomised, double-blind, parallel, placebo-controlled trial. *Lancet Neurology* 2010;**9**(9):855–65. [MEDLINE: 20688574]

Wald 2002
Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. *BMJ* 2002;**325**(7374):1202. [MEDLINE: 1244653]

Weiner 2004
Weiner DE, Tighiouart H, Amin MG, Stark PC, MacLeod B, Griffith JL, et al. Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. *Journal of the American Society of Nephrology* 2004;**15**(5):1307–15. [MEDLINE: 15100371]

Wrone 2001
Wrone EM, Zehnder JL, Hornberger JM, McCann LM, Coplon NS, Fortmann SP. An MTHFR variant, homocysteine, and cardiovascular comorbidity in renal disease. *Kidney International* 2001;**60**(3):1106–13. [MEDLINE: 11532106]

Yang 2012

Yang J, Hu X, Zhang Q, Cao H, Wang J, Liu B. Homocysteine level and risk of fracture: A meta-analysis and systematic review. *Bone* 2012;**51**(3):376–82. [MEDLINE: 22749888]

Zoccali 2010

Zoccali C, Jager KJ. Hyperhomocysteinemia: a renal and cardiovascular risk factor?. *Nature Reviews Nephrology* 2010; **6**(12):695–6. [MEDLINE: 21109767]

References to other published versions of this review

Nigwekar 2009

Nigwekar SU, Cass A, Gallagher MP, Jardine MJ, Kang A, Kulshrestha S, et al. Interventions for lowering plasma homocysteine levels in dialysis patients. *Cochrane Database of Systematic Reviews* 2009, Issue 2. [DOI: 10.1002/14651858.CD004683.pub3]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ASFAST 2004

Methods	• Study design: parallel RCT • Study duration: 30 June 1998 to 31 December 2000, median follow-up 3.6 years • Completeness of follow-up-specific information regarding dialysis population not available; however, overall 4 patients of 315 were lost to follow-up • Withdrawal of consent-specific information regarding dialysis population not available; however, overall 32 patients of 315 withdrew consent
Participants	• Setting: 5 outpatient dialysis units • Country: Australia and New Zealand • Relevant health status: CKD of any cause, SCr $\geq$ 0.40 mmol/L and awaiting commencement of dialysis or on CAPD, intermittent PD or HD • Number: treatment group (136); control group (131) • Mean age ± SD (years) (specific information regarding dialysis population not available): treatment group (56 ± 13); control group (56 ± 14) • Sex (male) (specific information regarding dialysis population not available): treatment group (73%); control group (62%) • Exclusion criteria: inability to obtain informed consent; inability to comply with study protocol; planned early living-related transplantation; presence of a life threatening disease such as cancer; state of high cell turnover such as inflammatory bowel disease; ongoing treatment with methotrexate; phenytoin, or trimethoprim-sulphamethoxazole; recent return to dialysis after transplantation and still on immunosuppression; cobalamin deficiency without replacement; previous bilateral carotid artery surgery or carotid artery stenosis > 75% on screening
Interventions	Treatment group • Folic acid • 15 mg oral daily for median duration of 3.6 years Control group • Identical appearing placebo daily for median duration of 3.6 year Co-interventions • None
Outcomes	• Change in rate of progression of mean maximum carotid artery intimal media thickness, composite of MI, stroke, and death from cardiovascular cause • All fatal and nonfatal cardiovascular events including MI, stroke, unstable angina, revascularisation, and peripheral vascular disease
Notes	• Funding source: National Health and Medical Research Council of Australia and National Heart Foundation of New Zealand • Study authors were contacted and additional information obtained • Other: mandatory folic acid fortification was not present in Australia and New Zealand at the time of this study

Risk of bias

ASFAST 2004 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	RCT with random sequence generation
Allocation concealment (selection bias)	Low risk	Study medication dispensed in identical containers with neither study staff nor participant aware of treatment allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind RCT
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All clinical end points were subject to an independent adjudication process by an endpoint monitoring committee. Carotid intimal-medial thickness measurements were performed in the same study laboratory in each major city centre and a single reference laboratory performed all image analyses
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data on mortality and morbidity available for 99% of participants; data analysed per intention to treat
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	Low risk	The study appears to be free of other bias

Heinz 2009

Methods	• Study design: parallel RCT • Study duration: July 2002 to July 2008, median follow-up 2.1 years • Completeness of follow-up: of 650 patients, 107 received transplant, 75 withdrew from participation, and 18 discontinued treatment because of change in dialysis centre • Withdrawal of consent: 75 withdrew from participation
Participants	• Setting: 33 outpatient dialysis units • Country: Germany • Relevant health status: ESKD treated for at least one month by HD • Number: treatment group (327); control group (323) • Mean age ± SD (years): treatment group (61 ± 13); control group (61 ± 13) • Sex (male): treatment group (58%); control group (59%) • Exclusion criteria: acute coronary events within 6 weeks before randomisation; active malignant tumour; pregnancy; lactation; addiction to drugs or alcohol

Heinz 2009 (*Continued*)

Interventions	Treatment group • 5 mg folic acid, 50 µg B_{12}, 20 mg B_6 orally after each HD session for a median follow-up of 2.1 years • Taken under nurse supervision Control group • 0.2 mg folic acid, 4 µg B_{12}, 1 mg B_6 orally after each HD session for a median follow-up of 2.1 years • Taken under nurse supervision Co-interventions • None
Outcomes	• Total mortality • Occurrence of first fatal or nonfatal cardiovascular event (MI, unstable angina, coronary vascularisation procedure, sudden cardiac death, stroke, peripheral artery disease, PE, and thromboses). Shunt thromboses were not regarded as an end point
Notes	• Funding source: School of Medicine of Otto-von-Guericke University Magdeburg; Roche diagnostics, Mannheim, Germany and Fresenius Medical Care, Bad Homburg, Germany • Study authors contacted for additional information but no additional information was obtained • Other: mandatory folic acid fortification was not present in Germany at the time of this study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	RCT but sequence generation unclear
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind RCT
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Mortality data available on all patients
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	Low risk	The study appears to be free of other bias

HOST Study 2004

Methods	• Study design: parallel RCT • Study duration: recruitment from September 2001 to October 2003, median follow-up 3.2 years • Completeness of follow-up: specific information regarding dialysis population not available; however, of 2056 randomised patients, 169 withdrew from regular telephone follow-up but continued to allow medical record review, and 66 withdrew consent from follow-up contacts and medical record review • Withdrawal of consent: specific information regarding dialysis population not available; however, of 2056 randomised patients, 66 withdrew consent from follow-up contacts and medical record review
Participants	• Setting: 36 participating outpatient VA medical centres • Country: USA • Relevant health status: ESKD on maintenance HD or PD, or with an estimated CrCl $\leq$ 30 mL/min and plasma homocysteine level $\geq$ 15 µmol/L. For this review only patients with ESKD were included • Number: treatment group (372); control group (379) • Mean age ± SD (years) (specific information regarding dialysis population not available): treatment group (65 ± 12); control group (66 ± 12) • Sex (male) (specific information regarding dialysis population not available): treatment group (98%); control group (98%) • Exclusion criteria: age < 21 years; expected life span < 6 months; pregnancy; metastatic cancer; end-stage liver disease; treatment with methotrexate; other antifolate medication or anticonvulsants; unreliable or likely noncompliant participation in another long-term RCT or unwilling or unable to give informed consent
Interventions	Treatment group • 40 mg folic acid, 100 mg vitamin B_6, 2 mg vitamin B_{12} daily for a median follow-up of 3.2 years Control group • Identical: appearing placebo daily for a median follow-up of 3.2 years Co-interventions • Participants in both groups were permitted to take additional vitamins containing no more than 1 mg of folate if prescribed by their physicians as part of their routine medical care
Outcomes	• Time to death from any cause • Time to MI, stroke, amputation of all or part of a lower extremity, and a composite of these three plus all-cause mortality
Notes	• Funding source: Co-operative Studies program, Department of Veterans Affairs Office of Research and Development. Abbott Laboratories donated the homocysteine analytic kits. The VA Palo Alto Health Care System received payment from Pam-Lab for performing chemical analyses, including the salary of a research technician and for supplies • Study authors contacted for additional information but no additional information was obtained • Mandatory folic acid fortification was present in the USA at the time of this study

HOST Study 2004 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random permuted block design of varying block size
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind RCT
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	For primary outcome all patients were counted. For secondary outcome analyses, 32 ESKD patients (from 751) were censored due to study withdrawal
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	Low risk	The study appears to be free of other bias

Righetti 2003

Methods	• Study design: parallel RCT • Study duration: January 2001 to December 2003, median follow-up 2.4 years • Completeness of follow-up: of 114 patients, none were lost to follow-up • Withdrawal of consent: none withdrew from participation
Participants	• Setting: outpatient single centre study • Country: Italy • Relevant health status: ESKD treated for at least 4 months by HD • Number: treatment group (37); control group (51) • Mean age ± SD (years): treatment group (63.9 ± 1.6); control group (65.1 ± 1.9) • Sex (male): treatment group (65%); control group (49%) • Exclusion criteria: treatment with theophylline, oestrogens or anti-epileptic medications
Interventions	Treatment group • 5 mg folic acid orally daily (every other day if serum folic acid > 16.8 ng/mL) along with an oral vitamin B complex (thiamine 250 mg, pyridoxine 250 mg and cyanocobalamin 500 mg every other day) for a median follow-up of 871 days Control group • Identical appearing placebo for a median follow-up of 871 days

Righetti 2003 (*Continued*)

	Co-interventions • None
Outcomes	• Composite cardiovascular endpoint (typical history of angina with abnormal myocardial scintigraphy or coronarography, fatal and nonfatal MI, symptomatic extracranial carotid stenosis resulting in carotid endarterectomy, fatal and nonfatal stroke and sudden cardiac arrest)
Notes	• Funding source: not provided • Study authors contacted for additional information but no additional information was obtained • Mandatory folic acid fortification was not present in Italy at the time of this study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Independent person performed randomisation using a box containing blind numbers
Allocation concealment (selection bias)	Low risk	Independent person performed randomisation using a box containing blind numbers
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open RCT
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data complete
Selective reporting (reporting bias)	Unclear risk	Composite outcome reported
Other bias	High risk	No wash out period for group A, significant differences in baseline variables

Vianna 2007

Methods	• Study design: parallel RCT • Study duration: April 2003 to March 2005, follow-up 2 years • Completeness of follow-up: no patients were lost to follow-up. All patients were alive and examined at 6 months; between 6 and 24 months, 15 patients were transplanted and 53 died • Withdrawal of consent: 75 withdrew from participation
Participants	• Setting: single centre outpatient study • Country: Brazil • Relevant health status: ESKD patients who were stable on HD 3 times/week for at least 4 months • Number: treatment group (93); control group (93) • Mean age ± SD (years): treatment group (49.3 ± 13.5); control group (47.6 ± 12.3) • Sex (male): treatment group (60%); control group (58%) • Exclusion criteria: a potential kidney transplant from a living donor in the next three months; class IV heart failure; unstable angina; indication for coronary revascularisation; recent cerebrovascular accident; cancer; and ongoing hospitalisation
Interventions	Treatment group • Oral folic acid 10 mg 3 times/week after dialysis sessions for 2 years • Under nurse supervision Control group • Identical appearing placebo after dialysis sessions for 2 years • Under nurse supervision Co-interventions • None
Outcomes	• Primary end point was a composite of new major cardiovascular events, including death from cardiovascular causes, nonfatal MI, cardiac arrhythmias, angina, heart failure, and cerebral vascular accident • Secondary end point was the evaluation of the IMT of the common carotid arteries
Notes	• Funding source: grant from Araucaria Foundation, a Parana State Government Agency • Study authors contacted for additional information but no additional information was obtained • Mandatory folic acid fortification was not present in Brazil at the time of this study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Vianna 2007 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind RCT with participants and personnel blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded fashion interpretation of secondary outcomes mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patient lost to follow-up
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	Low risk	The study appears to be free of other bias

Wrone 2004

Methods	• Study design: parallel RCT • Study duration: March 1998 to May 1999 • Completeness of follow-up: patients terminated study interventions for the following reasons: death (189), received kidney transplant (58), moved away (37), and return of kidney function (2). There was no differential dropout among the treatment arms. Eight patients discontinued study medication due to side effects, which included nausea, abdominal discomfort, "hunger and weight gain" • Withdrawal of consent: 8 patients discontinued study medication due to side effects, which included nausea, abdominal discomfort, "hunger and weight gain." The side effects were equally distributed among the treatment arms
Participants	• Setting: 10 affiliated non-profit outpatient dialysis facilities • Country: USA • Relevant health status: patients undergoing HD or PD • Number: treatment group 1 (176); treatment group 2 (166); control group (168) • Mean age ± SD (years): treatment group 1(59.8 ± 15.4), treatment group 2 (59.5 ± 15.4); control group (61.3 ± 14.6) • Sex (male): treatment group 1 (51.1%); treatment group 2 (48.9%), control group (50%) • Exclusion criteria: patients undergoing intradialytic parenteral nutrition; anticipating a living-related kidney transplant; receiving an anti-seizure medication; residing in an institution; terminally ill
Interventions	Treatment group 1 • Renal multivitamin containing 5 mg of folic acid orally once daily for a median follow-up of 2 years Treatment group 2 • Renal multivitamin containing 15 mg of folic acid orally once daily for a median follow-up of 2 years Control group • Renal multivitamin containing 1 mg folic acid orally once daily for a median

Wrone 2004 (*Continued*)

	follow-up of 2 years Co-interventions • All capsules contained: 12.5 mg pyridoxine, 6 μg cobalamin, 60 mg ascorbic acid, 1.5 mg thiamine, 20 mg niacinamide, 10 mg pantothenic acid, and 0.3 mg biotin
Outcomes	• Cardiovascular events (coronary artery intervention, MI, stroke, transient ischaemic attack, carotid endarterectomy, limb amputation) and mortality • Vascular access thrombosis (among those with AV fistulae)
Notes	• Funding source: Study multivitamins were provided by R&D Laboratories, Inc., Marina del Rey, CA. This donor did not contribute to study design, data collection, analysis, interpretation of the data, or the decision to approve the manuscript • Study authors contacted for additional information but no additional information was obtained • Mandatory folic acid fortification was present in United States at the time of this study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Randomisation codes were kept in a separate, locked file
Blinding of participants and personnel (performance bias) All outcomes	Low risk	To maintain double-blind status, neither the person performing the randomisation nor the person preparing study medication for distribution to clinical coordinators had direct contact with participants. Patients, clinicians, and study staff with patient contact did not have access to any information that could identify treatment arm
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	18 patients of 588 did not receive intervention and were not analysed
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	Low risk	The study appears to be free of other bias

AV - arteriovenous; CAPD - continuous ambulatory peritoneal dialysis; CKD - chronic kidney disease; CrCl - creatinine clearance; ESKD - end-stage kidney disease; HD - haemodialysis; IMT - intima-media wall thickness; MI - myocardial infarction; PD - peritoneal dialysis; PE - pulmonary embolism; RCT - randomised controlled trial; SCr - serum creatinine; SD - standard deviation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ali 2003	Intervention's primary action is not homocysteine lowering
Alvares Delfino 2007	< 100 patient-years
Anderson 2006	< 100 patient-years
Ardalan 2003	< 100 patient-years
Ardalan 2003a	Kidney transplant not dialysis patients
Armada 2003	< 100 patient-years
Arnadottir 2003	< 100 patient-years
ATIC Study 2005	Multiple interventions and < 100 patient-years
Azadibakhsh 2007	< 100 patient-years
Beavers 2008	Not homocysteine lowering
Bennett-Richards 2002	Cross-over or sequential design
Bostom 1996	< 100 patient-years
Bostom 2000	< 100 patient-years
Branley 2000	< 100 patient-years
Brensing 2002	< 100 patient-years
Brensing 2003	< 100 patient-years
Chang 2007	< 100 patient-years
Chiu 2009	< 100 patient-years
Cianciolo 2008	Compares different formulations
Cutler 2009	< 100 patient-years

(*Continued*)

De Angelis 2007	< 100 patient-years
De Vecchi 2001	< 100 patient-years
De Vriese 2003	Sequential or cross-over design
Del Pozo 2005	< 100 patient-years
Dierkes 1999	< 100 patient-years
Dierkes 2001	< 100 patient-years
DIVINe Study 2010	Population: diabetic nephropathy
Dobronravov 2008	< 100 patient-years
Ducloux 2002	< 100 patient-years
Elian 2002	< 100 patient-years
Friedman 2003	< 100 patient-years
Galli 2003	< 100 patient-years
Gonin 2003	< 100 patient-years
Gonin 2003a	< 100 patient-years
Hauser 2001	< 100 patient-years
Henning 2001	< 100 patient-years
Hoffer 2005	< 100 patient-years
Hoffer 2005a	< 100 patient-years
HOPE-2 Study 2006	Population: CKD
House 1999	< 100 patient-years
House 2004	Not folic acid-based homocysteine lowering
Imani 2009	Not folic acid-based homocysteine lowering
Isbel 2003	< 100 patient-years

(*Continued*)

ISRCTN22151635	Not folic acid-based homocysteine lowering
Jara 2001	< 100 patient-years
Kazory 2008	Not folic acid-based homocysteine lowering
Klemm 2004	Not proven homocysteine lowering treatment
Kooshki 2011	< 100 patient-years
Koyama 2002	< 100 patient-years
Koyama 2010	< 100 patient-years
Kuhlmann 2004	< 100 patient-years
Kumar 2007b	Cross-over study
Kuo 2001a	< 100 patient-years
LANDMARK Study 2006	Multiple interventions
Libetta 2004	< 100 patient-years
Madsen 2011	Primary mechanism is not homocysteine lowering
Manns 2001	< 100 patient-years
Mazdeh 2005	< 100 patient-years
McGregor 2000a	< 100 patient-years
Mudge 2005	< 100 patient-years
Mueller 2001	< 100 patient-years
Muller 2001	< 100 patient-years
Nakamura 2003	Not an intervention study
Nakhoul 2004	< 100 patient-years
Nascimento 2010	No pre-specified outcome data
OPACH Study 2006	Intervention with other effects other than homocysteine lowering

(*Continued*)

Ossareh 2009	< 100 patient-years
Pakfetrat 2013	< 100 patient-years
Pastore 2006	< 100 patient-years
Peng 2005	< 100 patient-years
Polkinghorne 2003	< 100 patient-years
Poulia 2011	< 100 patient-years
Sanchez Alvarez 2005	< 100 patient-years
Scholze 2004	N-acetylcysteine study: intervention with multiple other effects other than homocysteine lowering
Seo 2003	< 100 patient-years
Sepe 1999	< 100 patient-years
Shemin 2001	Review article
Signorelli 2006	Intervention with no proven effects on homocysteine lowering
Skoutakis 1975	Not homocysteine lowering study
Stavrianaki 2002	< 100 patient-years
Tamadon 2011	< 100 patient-years
Tayyebi-Khosroshahi 2010	Primary mechanism is not homocysteine lowering
Tepel 2003	N-acetylcysteine study: intervention with multiple other effects other than homocysteine lowering
Thaha 2006	< 100 patient-years
Thaha 2008	< 100 patient-years
Thaha 2009	Cross-over study
Thambyrajah 2000	< 100 patient-years
Tobe 1999	< 100 patient-years
Tochihara 2008	No pre-specified outcomes
Treleaven 2001	No pre-specified outcomes

(*Continued*)

Tremblay 2000	< 100 patient-years
Trimarchi 2002	< 100 patient-years
Tungkasereerak 2006	< 100 patient-years
Urquhart 2008	< 100 patient-years
van Guldener 1998	No pre-specified outcomes
Van Tellingen 2001	No pre-specified outcomes
VIENNA Study 2000	No pre-specified outcomes
Vrentzos 2001	No pre-specified outcomes
Vychytil 2003	< 100 patient-years
Westphal 2001	Intervention with multiple effects in addition to homocysteine lowering
Yango 2001	< 100 patient-years
Zeman 2006	< 100 patient-years
Zuo 2001	< 100 patient-years

CKD - chronic kidney disease

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT00004495

Methods	This is an RCT. Patients are stratified according to pre-study homocysteine levels (above or below average). Patients are randomised to receive placebo or one of two doses of oral folic acid, with or without pyridoxine and cyanocobalamin Arm I: Patients receive oral placebo daily. Arm II: Patients receive oral pyridoxine, cyanocobalamin, and oral placebo daily Arm III: Patients receive oral pyridoxine, cyanocobalamin, and folic acid daily Arm IV: Patients receive oral pyridoxine and cyanocobalamin plus a higher dose of folic acid daily Arm V: Patients receive oral placebo and oral folic acid daily Arm VI: Patients receive oral placebo and higher dose folic acid daily Treatment continues for 8 weeks
Participants	Ages eligible for study: 21 to 89 years Genders eligible for study: both Accepts healthy volunteers: no

NCT00004495 (*Continued*)

	Entry criteria Disease characteristics: diagnosis of ESKD requiring regular HD treatment 3 times weekly; baseline predialysis total homocysteine concentration in plasma greater than 16 µmol/L; no prior or concurrent pernicious anaemia; no blood smear examination showing unexplained macrocytosis Prior/concurrent therapy Chemotherapy: no concurrent chemotherapy for cancer Other: no concurrent levodopa or carbidopa; no concurrent penicillamine or trimethoprim-sulphonamide combination; no concurrent antiviral therapy No concurrent anticonvulsants Patient characteristics Hematopoietic: HCT at least 25% Other: not pregnant or nursing Negative pregnancy test; fertile patients must use effective contraception; no Parkinson's disease; no convulsions or epilepsy requiring treatment; no lactose intolerance or allergy to milk products; no history of allergic sensitization following administration of folic acid, pyridoxine (vitamin B_6), or cyanocobalamin (vitamin B_{12}); no vitamin B_{12} concentration below lower limit of normal (150 pmol/L); no untreated hypothyroidism or psoriasis
Interventions	Patients are randomised to receive placebo or one of two doses of oral folic acid, with or without pyridoxine and cyanocobalamin Arm I: Patients receive oral placebo daily Arm II: Patients receive oral pyridoxine, cyanocobalamin, and oral placebo daily Arm III: Patients receive oral pyridoxine, cyanocobalamin, and folic acid daily Arm IV: Patients receive oral pyridoxine and cyanocobalamin plus a higher dose of folic acid daily Arm V: Patients receive oral placebo and oral folic acid daily Arm VI: Patients receive oral placebo and higher dose folic acid daily Treatment continues for 8 weeks
Outcomes	Objectives I. Compare the efficacy of two doses of folic acid in normalizing plasma total homocysteine concentration in patients with ESKD receiving regular HD therapy resulting in hyperhomocysteinaemia II. Determine the requirement of co-supplementation with extra pyridoxine (vitamin B_6) and cyanocobalamin (vitamin B_{12}) daily in these patients III. Assess the safety and tolerability of this therapy in these patients
Notes	

Soleimani 2011

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Tayebi-Khosroshahi 2013

Methods	
Participants	
Interventions	
Outcomes	
Notes	

ESKD - end-stage kidney disease; HCT - haematocrit; HD - haemodialysis

DATA AND ANALYSES

Comparison 1. Primary outcome

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cardiovascular mortality	4	1186	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.70, 1.22]

Comparison 2. Secondary outcomes

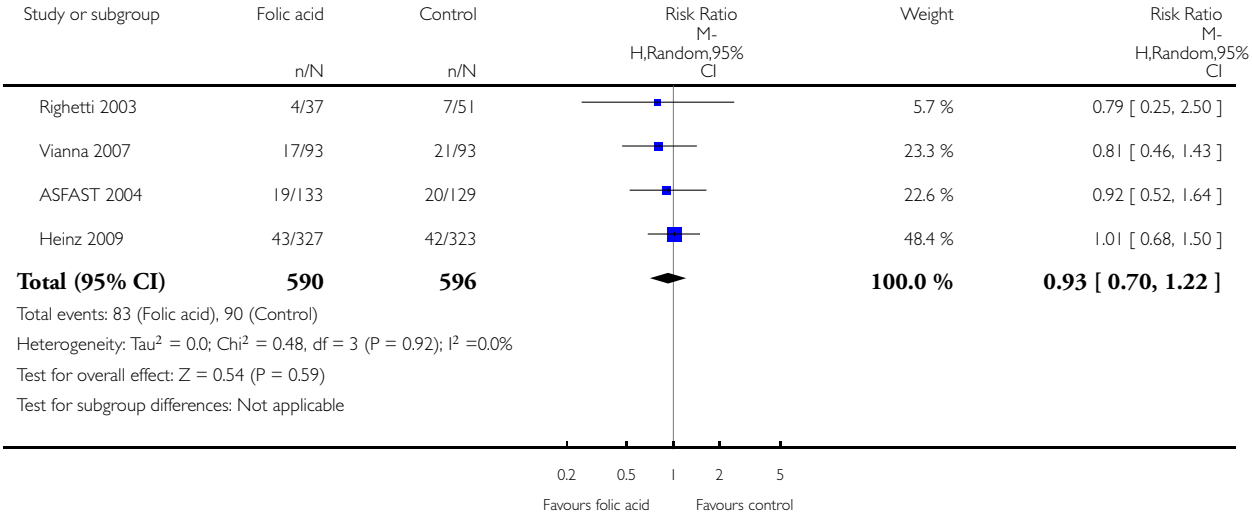
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	6	2447	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.89, 1.11]
2 Myocardial infarction (fatal and non fatal)	4	1510	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.66, 1.62]
3 Coronary revascularisation	2	1160	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.22, 3.14]
4 Stroke	4	1510	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.57, 1.40]
5 Deep venous thrombosis and pulmonary embolism	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6 Thrombosis of dialysis access	2	1261	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.88, 1.14]
7 Adverse events	3	1248	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.51, 2.47]

Analysis 1.1. Comparison 1 Primary outcome, Outcome 1 Cardiovascular mortality.

Review: Interventions for lowering plasma homocysteine levels in dialysis patients

Comparison: 1 Primary outcome

Outcome: 1 Cardiovascular mortality



Analysis 2.1. Comparison 2 Secondary outcomes, Outcome 1 All-cause mortality.

Review: Interventions for lowering plasma homocysteine levels in dialysis patients

Comparison: 2 Secondary outcomes

Outcome: 1 All-cause mortality

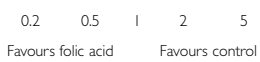
Study or subgroup	Folic acid n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Righetti 2003	6/37	12/51		1.6 %	0.69 [0.28, 1.67]
Vianna 2007	23/93	30/93		5.8 %	0.77 [0.48, 1.22]
Wrone 2004	105/342	56/168		17.4 %	0.92 [0.71, 1.20]
ASFAST 2004	39/133	37/129		8.6 %	1.02 [0.70, 1.49]
HOST Study 2004	159/372	158/379		44.3 %	1.03 [0.87, 1.21]
Heinz 2009	102/327	92/323		22.2 %	1.10 [0.86, 1.39]
Total (95% CI)	**1304**	**1143**		**100.0 %**	**1.00 [0.89, 1.11]**

Total events: 434 (Folic acid), 385 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.99$, df = 5 (P = 0.70); $I^2 = 0.0\%$

Test for overall effect: Z = 0.05 (P = 0.96)

Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2 Secondary outcomes, Outcome 2 Myocardial infarction (fatal and non fatal).

Review: Interventions for lowering plasma homocysteine levels in dialysis patients

Comparison: 2 Secondary outcomes

Outcome: 2 Myocardial infarction (fatal and non fatal)

Study or subgroup	Folic acid n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
ASFAST 2004	8/133	7/129		20.6 %	1.11 [0.41, 2.97]
Heinz 2009	20/327	19/323		53.9 %	1.04 [0.57, 1.91]
Righetti 2003	3/37	5/51		10.7 %	0.83 [0.21, 3.25]
Wrone 2004	9/342	4/168		14.8 %	1.11 [0.35, 3.54]
Total (95% CI)	**839**	**671**		**100.0 %**	**1.04 [0.66, 1.62]**

Total events: 40 (Folic acid), 35 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.13$, df = 3 (P = 0.99); $I^2 = 0.0\%$

Test for overall effect: Z = 0.16 (P = 0.87)

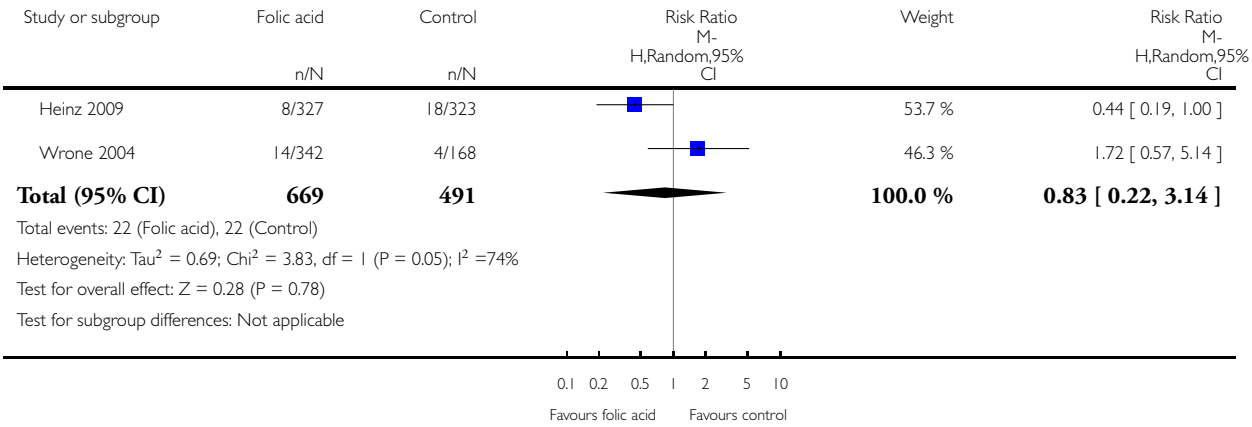
Test for subgroup differences: Not applicable

Analysis 2.3. Comparison 2 Secondary outcomes, Outcome 3 Coronary revascularisation.

Review: Interventions for lowering plasma homocysteine levels in dialysis patients

Comparison: 2 Secondary outcomes

Outcome: 3 Coronary revascularisation

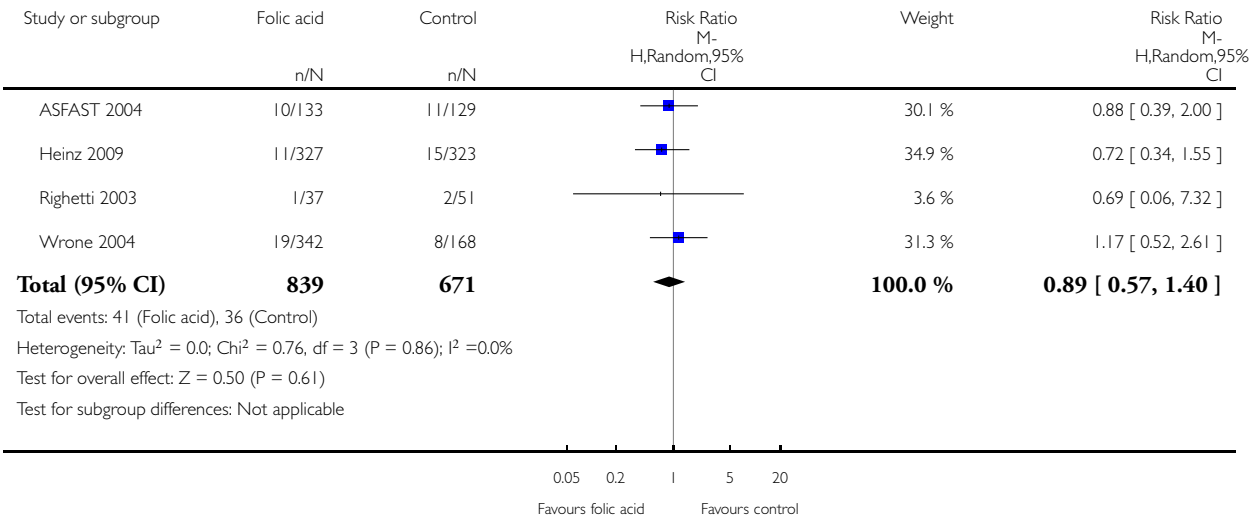


Analysis 2.4. Comparison 2 Secondary outcomes, Outcome 4 Stroke.

Review: Interventions for lowering plasma homocysteine levels in dialysis patients

Comparison: 2 Secondary outcomes

Outcome: 4 Stroke

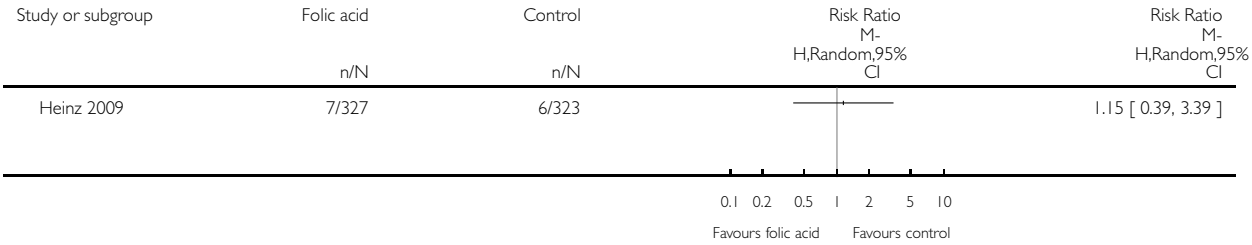


Analysis 2.5. Comparison 2 Secondary outcomes, Outcome 5 Deep venous thrombosis and pulmonary embolism.

Review: Interventions for lowering plasma homocysteine levels in dialysis patients

Comparison: 2 Secondary outcomes

Outcome: 5 Deep venous thrombosis and pulmonary embolism

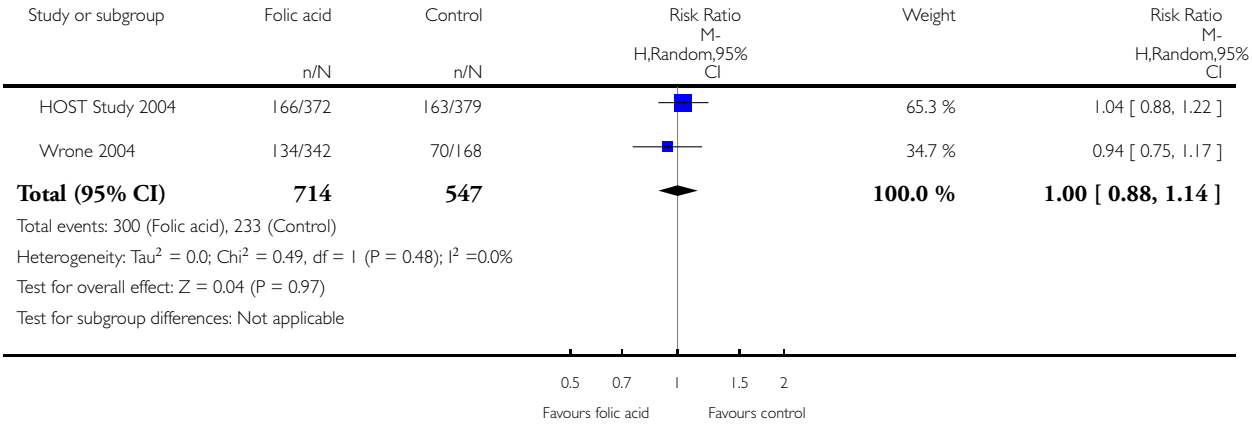


Analysis 2.6. Comparison 2 Secondary outcomes, Outcome 6 Thrombosis of dialysis access.

Review: Interventions for lowering plasma homocysteine levels in dialysis patients

Comparison: 2 Secondary outcomes

Outcome: 6 Thrombosis of dialysis access

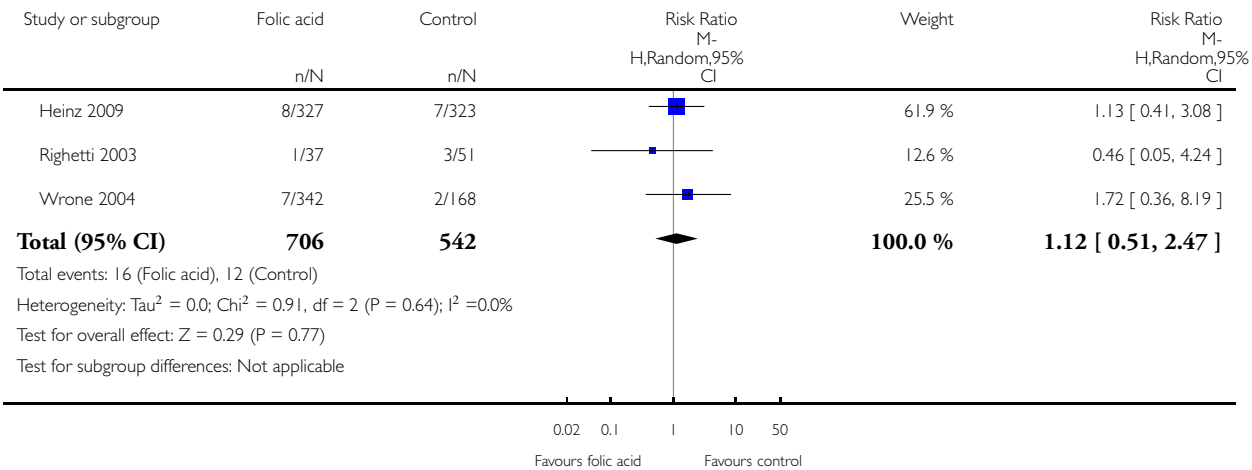


Analysis 2.7. Comparison 2 Secondary outcomes, Outcome 7 Adverse events.

Review: Interventions for lowering plasma homocysteine levels in dialysis patients

Comparison: 2 Secondary outcomes

Outcome: 7 Adverse events



APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor Homocysteine explode all trees 2. MeSH descriptor Hyperhomocysteinemia, this term only 3. homocysteine* in Clinical Trials 4. hyperhomocysteine* in Clinical Trials 5. (#1 OR #2 OR #3 OR #4) 6. MeSH descriptor Renal Replacement Therapy explode all trees 7. MeSH descriptor Renal Insufficiency, this term only 8. MeSH descriptor Renal Insufficiency, Chronic explode all trees 9. MeSH descriptor Kidney Failure, this term only 10. MeSH descriptor Kidney Diseases, this term only 11. "end-stage renal" or "end-stage kidney" or "endstage renal" or "endstage kidney" in Clinical Trials 12. ESRF or ESKF or ESRD or ESKD in Clinical Trials 13. "chronic kidney" or "chronic renal" in Clinical Trials 14. CKF or CKD or CRF or CRD in Clinical Trials 15. dialysis* in Clinical Trials 16. haemodialysis or haemodialysis in Clinical Trials 17. haemofiltration or haemofiltration in Clinical Trials 18. haemodiafiltration or haemodiafiltration in Clinical Trials 19. PD or CAPD or CCPD or APD in Clinical Trials 20. (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19) 21. (#5 AND #20)
MEDLINE	1. exp Homocysteine/ 2. Hyperhomocysteinemia/ 3. hyperhomocysteine$.tw. 4. homocystein$.tw. 5. or/1-4 6. exp Renal Replacement Therapy/ 7. Renal Insufficiency/ 8. exp Renal Insufficiency, Chronic/ 9. Kidney Failure/ 10. Kidney Diseases/ 11. Diabetic Nephropathies/ 12. (kidney disease$ or kidney failure$ or renal disease$ or renal failure$).tw. 13. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.

(*Continued*)

	14. (ESRF or ESKF or ESRD or ESKD).tw. 15. (chronic kidney or chronic renal).tw. 16. (CKF or CKD or CRF or CRD).tw. 17. dialysis.tw. 18. (hemodialysis or haemodialysis).tw. 19. (hemodiafiltration or haemodiafiltration).tw. 20. (hemofiltration or haemofiltration).tw. 21. (PD or CAPD or CCPD or APD).tw. 22. Diabetic nephropath$.tw. 23. or/6-22 24. and/5,23
EMBASE	1. Homocysteine/ 2. Hyperhomocysteinemia/ 3. hyperhomocysteine$.tw. 4. homocystein$.tw. 5. or/1-4 6. exp renal replacement therapy/ 7. exp Kidney Transplantation/ 8. Diabetic Nephropathy/ 9. chronic kidney disease/ 10. kidney disease/ 11. (kidney disease$ or kidney failure$ or renal disease$ or renal failure$).tw. 12. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw. 13. (ESRF or ESKF or ESRD or ESKD).tw. 14. (chronic kidney or chronic renal).tw. 15. (CKF or CKD or CRF or CRD).tw. 16. dialysis.tw. 17. (hemodialysis or haemodialysis).tw. 18. (hemodiafiltration or haemodiafiltration).tw. 19. (hemofiltration or haemofiltration).tw. 20. (PD or CAPD or CCPD or APD).tw. 21. diabetic nephropath$.tw.

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random)

(*Continued*)

	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention
	Unclear: Insufficient information about the sequence generation process to permit judgement
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes)
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure
	Unclear: Randomisation stated but no information on method used is available
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding

(*Continued*)

	could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub-scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome

(*Continued*)

	that would be expected to have been reported for such a study
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias

HISTORY

Protocol first published: Issue 1, 2004

Review first published: Issue 5, 2016

Date	Event	Description
11 December 2008	New citation required and major changes	New authors
1 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: AC, MG, MJ, AK, SK, SDN, SN, TN, VP
2. Study selection: MJ, AK, SK, SDN, SN, VP,
3. Extract data from studies: MJ, SK, SDN, SN, VP
4. Enter data into RevMan: MJ, SN
5. Carry out the analysis: MJ, SK, SDN, SN, TN, VP
6. Interpret the analysis: MJ, SK, SDN, SN, TN, VP, GS, SZ
7. Draft the final review: MJ, SK, SDN, SN, TN, VP
8. Disagreement resolution: AC, MG, MJ, AK, SK, SDN, SN, TN, VP, GS, SZ
9. Update the review: AC, MG, MJ, AK, SK, SDN, SN, TN, VP, GS, SZ

DECLARATIONS OF INTEREST

- Sagar U Nigwekar: none known
- Amy Kang: none known
- Sophia Zoungas: I have received speaker honoria from Servier, MSD, Novo Nordisk, Sanofi Aventis, Johnson and Johnson and Astra Zeneca/BMS. I have served on external advisory boards for MSD, Amgen, AbbVie, Novo Nordisk, Novartis, Takeda, Sanofi Aventis and Astra Zeneca.
- Alan Cass: The Menzies School of Health Research has received unconditional research funding from AMGEN, Merck and Novartis for research in chronic kidney disease in Indigenous populations
- Martin P Gallagher: Martin Gallagher has received competitive research funding from the Royal Australasian College of Physicians and the Australian National Health and Medical Research Council in the last 36 months.
- Satyarth Kulshrestha: none known
- Sankar D Navaneethan: none known
- Vlado Perkovic: none known
- Giovanni FM Strippoli: Institutional support from AIfa-italian medicines agenda for Cedose trial funding (ESA dose); employment by Diaverum, renal service provider for dialysis
- Meg J Jardine: is supported by a NHMRC Career Development Fellowship and National Heart Foundation Future Leader Fellowship.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Clinical Scientist in Nephrology award from the American Kidney Fund, USA.

Sagar U Nigwekar

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol, we mentioned N-acetyl cysteine as an intervention that lowers serum homocysteine levels to be considered for this review. Although it has this effect there are significant other effects including anti-oxidant effects from this intervention and since this review is focused on interventions that primarily reduce homocysteine, we decided to not include studies that evaluated N-acetyl cysteine in the ESKD setting in this review. Our search identified only four such studies (Ali 2003; Nascimento 2010; Scholze 2004; Tepel 2003; Thaha 2006).

INDEX TERMS

Medical Subject Headings (MeSH)

*Renal Dialysis; Cardiovascular Diseases [etiology; *mortality]; Cause of Death; Folic Acid [adverse effects; *therapeutic use]; Homocysteine [blood]; Hyperhomocysteinemia [*drug therapy]; Kidney Failure, Chronic [*blood; therapy]; Myocardial Infarction [epidemiology]; Stroke [epidemiology]; Venous Thrombosis [epidemiology]; Vitamin B 12 [therapeutic use]; Vitamin B 6 [therapeutic use]; Vitamin B Complex [*therapeutic use]

MeSH check words

Aged; Female; Humans; Male; Middle Aged