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[Intervention Review]

Interventions for lowering plasma homocysteine levels in kidney transplant recipients

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ABSTRACT

Background

Elevated homocysteine levels have been shown to be an independent risk factor for cardiovascular disease. However studies of homocysteine lowering in general and end-stage kidney disease (ESKD) populations have not demonstrated a reduction in cardiovascular event rates. Kidney transplant recipients have high homocysteine levels, high cardiovascular event rates and, unlike the ESKD population, may achieve normalisation of homocysteine levels with homocysteine lowering therapies. Thus may benefit from homocysteine lowering therapy.

Objectives

To evaluate the effects of established homocysteine lowering therapy on cardiovascular mortality in patients with functioning kidney transplants.

Search methods

We searched the Cochrane Renal Group's Specialised Register to 16 March 2015 through contact with the Trials' Search Co-ordinator using search terms relevant to this review.

Selection criteria

Randomised controlled trials of any therapy that has been shown to significantly lower homocysteine levels conducted in people with functioning kidney transplants. Studies were to be included if they compared homocysteine lowering therapy with placebo or usual care, or compare higher versus lower doses of homocysteine lowering therapy.

Data collection and analysis

Two authors independently assessed study quality and extracted data. Results were to be expressed as the risk ratio (RR) for dichotomous outcomes or mean difference (MD) for continuous outcomes with 95% confidence intervals (CI). Data was to be pooled using the random effects model.

Main results

The literature search yielded 359 reports of which only one study was identified that met our inclusion criteria and reported relevant clinical endpoints. This study randomised 4110 adult participants with a functioning kidney transplant and elevated homocysteine levels to folic acid plus high dose B multivitamins or low dose multivitamins who were followed for a mean 4.0 years. Despite effectively lowering homocysteine levels) in homocysteine levels at follow-up (MD -4.40 µmol/L, 95% CI -5.98 to -2.82) there was no evidence the intervention impacted on any of the outcomes reported including cardiovascular mortality (RR 0.91, 95% CI 0.69 to 1.20), all-cause mortality (RR 1.04, 95% CI 0.88 to 1.22), myocardial infarction (RR 1.02, 95% CI 0.77 to 1.35), stroke (RR 1.08, 95% CI 0.69 to 1.71), commencement of renal replacement therapy (RR 1.12, 95% CI 0.91 to 1.37) or all reported adverse events (RR 1.02, 95% CI 0.87 to 1.20). There was no evidence the intervention impacted on the primary endpoint of the study, a cardiovascular event composite (RR 0.99, 95% CI 0.85 to 1.15). The study was of high quality.

Authors' conclusions

There is no current evidence to support the use of homocysteine lowering therapy for cardiovascular disease prevention in kidney transplant recipients.

PLAIN LANGUAGE SUMMARY

Interventions for lowering plasma homocysteine levels in kidney transplant recipients

People with high homocysteine levels have higher rates of cardiovascular disease than those with homocysteine levels within the normal range. Kidney transplant recipients have proportionately more cardiovascular disease events than the general population. The aim of this review was to determine if homocysteine lowering therapies effectively reduce cardiovascular event rates in kidney transplant recipients. A single study was identified that randomised 4110 adult participants with a functioning kidney transplant to homocysteine lowering with folic acid and high dose multivitamins or to low dose multivitamins and followed them for an average of four years. Despite effectively lowering homocysteine levels, there was no evidence of benefit for any of a range of cardiovascular events. Similarly there was no evidence of harm.

BACKGROUND

Description of the condition

Kidney transplantation is the treatment of choice for end-stage kidney disease (ESKD), producing a life changing improvement in quality of life and adding approximately 10 years to the life expectancy of patients with ESKD on the transplant waiting list (NIH 2007). Despite the many developments in kidney transplantation over the last 50 years, recipients of kidney transplants continue to have an excess mortality and morbidity compared with the general population (NIH 2007). Cardiovascular disease (CVD) is a leading cause of death and late graft loss in kidney transplant recipients (Kasiske 1996; NIH 2007). In a recent report of a RCT in kidney transplant recipients with 20 years follow-up, cardiovascular deaths accounted for 53% of the total death rate (Gallagher 2009). Similar findings were reported by the large Assessment of Lescol in Renal Transplantation (ALERT) study (ALERT Study 2003). An observational cohort study has also reported the cumulative incidence of CVD 15 years after transplantation to be 23% for coronary artery disease, 15% for cerebrovascular disease and 15% for peripheral vascular disease (PVD) (Kasiske 1996). The overall risk of CVD following kidney transplantation is five times higher than that of the general population (Kasiske 1996).

Description of the intervention

In untreated classical homocysteinuria, a homozygous genetic disorder of C677T MTHFR resulting in very high levels of plasma homocysteine (100 to 400 µmol/L), death at a young age from venous thromboembolism and malignant arterial disease is frequently observed. Moreover, long-term treatments that lower homocysteine levels have been extremely effective in reducing the potentially life threatening vascular risk of these patients (Yap 2003). In addition, in the general population and Kidney transplant recipients high homocysteine levels has been shown to be an independent risk factor for CVD including stroke, myocardial infarction (MI), atherosclerosis, arterial and venous thrombosis and cardiovascular death in the general population (Ducloux 2000; HSC 2002; Massy 1994; Wald 2002). In kidney transplant recipients, every 1 µmol/L increase in total homocysteine is associated with a 6% increase in the risk of developing CVD, including MI, stroke, PVD and death (Ducloux 2000). Furthermore, hyperhomocysteinaemia has also been correlated to kidney allograft loss in kidney transplant recipients (Winkelmayer 2005). The striking benefits achieved in patients with homocysteinuria have long been speculated to also be reproducible in other general, chronic kidney disease (CKD) and kidney transplant recipients populations with elevated homocysteine levels. However interventions that lowered homocysteine levels have not yet been shown to reduce cardiovascular risk in either the CKD (Jamison 2007; Vianna 2007; Wrone 2004; Zoungas 2006) or in the general population (Albert 2008; Bonaa 2006; Lonn 2006; Schnyder 2002; Toole 2004).

How the intervention might work

Homocysteine is thought to play an active role in the pathogenesis of atherosclerosis by damaging the endothelium and promoting intra-arterial and venous thrombosis. There is strong experimental evidence that hyperhomocysteinaemia produces endothelial cell injury and proliferation of medial smooth muscle cells (Lang 2000; Lentz 1996; McCully 1996; Starkebaum 1986). In addition homocysteine has been found to enhance the activity of and increase the synthesis of clotting factors (D'Angelo 1997; Lentz 1991).

Why it is important to do this review

The role of homocysteine lowering in kidney transplant recipients has not been established. The kidney transplant recipient group may be the ideal group to test the homocysteine hypothesis as they have a high cardiovascular event rate (Kasiske 1996) and unlike the ESKD population, can achieve normal homocysteine levels with folic acid, vitamin B_{12}, and vitamin B_6 treatment (Beaulieu 1999).

The harms of homocysteine lowering interventions have also not been established. Whilst it is generally believed that folic acid, vitamin B_6 and B_{12} supplementation are safe, there are concerns that high folic acid levels may lead to increased cancer risk (Hubner 2007). This is of particular concern in the kidney transplant recipient group as they have higher absolute rates of malignancy than the general population. Thus even a small increase in relative risk of cancer may outweigh any potential benefits.

Efforts to reduce cardiovascular risk in kidney transplant recipients are attractive because of the large potential benefit of treatment. The European clinical guidelines (EBPG 2002) state the need for more research to be conducted as there is no evidence that reduction of homocysteine levels decreases the incidence of CVD in kidney transplant recipients.

This meta-analysis aims to assess the benefits and harms of homocysteine lowering therapy in kidney transplant recipients in order to guide decision making and improve outcomes for this patient population.

OBJECTIVES

To evaluate the effects of established homocysteine lowering therapy on cardiovascular mortality in patients with functioning kidney transplants.

METHODS

Criteria for considering studies for this review

Types of studies

1. Randomised controlled trials (RCTs) and quasi-RCTs (allocation to treatment was obtained by alteration, use of alternate medical records, date of birth or other predictable methods).
2. Including a minimum of 100 patient-years follow-up (to reduce the risk of reporting or publication bias).

Studies with a sequential or cross-over design were excluded.

Types of participants

All patients (adults and children) with a functioning kidney transplant defined as a kidney transplant in situ with no requirement for maintenance dialysis, or as defined by study authors.

Types of interventions

Studies randomising patients to any therapy which has been shown to significantly lower homocysteine levels were included (e.g. folic acid, vitamin B_6 and vitamin B_{12}). Studies of regimens

in which a major mechanism of action is not thought to be homocysteine lowering will be excluded (e.g. simvastatin plus folic acid). Comparisons to be investigated were as follows.

- Homocysteine lowering therapy versus placebo or usual care
- Higher 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 revascularization
- Cerebrovascular disease
  - Stroke
  - Cerebrovascular revascularization
- PVD and venous thromboembolic disease
  - Lower limb amputation
  - Deep vein thrombosis (DVT) and pulmonary embolism (PE)
- Kidney-specific outcomes
  - Commencement of renal replacement therapy (RRT) (dialysis or transplantation)
  - Change in kidney function
- 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 the Cochrane Renal Group's Specialised Register to 16 March 2015 through contact with the Trials' Search Co-ordinator using search terms relevant to this review. The Cochrane Renal Group's Specialised Register contains studies identified from the following sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of renal-related journals and the proceedings of major renal conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected renal 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 the Cochrane Renal Group. 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 Renal Group.

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

Searching other resources

1. Reference lists of clinical practice guidelines, review articles and relevant studies.
2. Experts in the field were contacted for additional studies.

Data collection and analysis

Selection of studies

Two authors independently assessed each reference for eligibility. Language was not an exclusion criterion. Disagreement regarding inclusion in the review was resolved by consensus among three authors.

Data extraction and management

Data extraction was performed independently by two authors using a standardised data form, who independently entered the data into RevMan 5. Where more than one publication of the study exists, the publications with the most complete data will be included. Where relevant outcomes were only published in earlier versions, these data were to be used. Any discrepancy between published versions was to be noted. The original author was to be contacted via written correspondence for any further information or clarification of unclear data. Disagreements were to be resolved by consensus among three authors.

Assessment of risk of bias in included studies

Two authors were to independently assess the following items 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 (detection bias)?
  - Participants and personnel
  - Outcome assessors
- 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 revascularization, cardiovascular death, stroke, cerebrovascular revascularization, lower limb amputation, DVT, PE, commencement of RRT), results were to be expressed as risk ratio (RR) with 95% confidence intervals (CI).

If a significant risk reduction was found, the absolute risk reduction with therapy was to be calculated in relation to the absolute risk found in the placebo/comparator group.

Dealing with missing data

Where outcomes sought were reported in insufficient detail to allow meta-analysis and further information was not forthcoming from triallists, these outcomes were to be tabulated and assessed with descriptive techniques and where possible the risk difference (RD) with 95% CI was to be calculated.

If sufficient RCTs were identified, an attempt was to be made to evaluate the risk of publication bias using a funnel plot. Attrition bias was to be assessed using the loss/event ratio.

Assessment of heterogeneity

Heterogeneity was to be 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% were taken to correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

The intention was that the risk of publication bias was to be evaluated using a funnel plot. Attrition bias was to be assessed using the loss/event ratio.

Data synthesis

The intention was that data was to be pooled using the random-effects model but the fixed-effect model would also be analysed to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were to be conducted to explore possible sources of heterogeneity. Heterogeneity was to be analysed using the Cochran Q test on N-1 degrees of freedom, with $P < 0.05$ used to denote statistical significance, and the I^2 test (with uncertainty intervals). Subgroup analyses were to be conducted according to the following characteristics.

- Gender
- Adults and children
- History of cardiac disease or diabetes mellitus
- Prior vitamin supplementation
- Concurrent vitamin supplementation
- Concomitant medications (e.g. aspirin)
- Mandatory grain fortification in the country study conducted
- Baseline homocysteine level (≤ upper limit normal (ULN) versus > ULN).

We intended to conduct a subgroup analysis if possible using these characteristics. Plausible explanations for variations in treatment effect were to be explored using subgroup analyses based on study quality and length of follow-up.

Sensitivity analysis

Sensitivity analyses were to be conducted to ensure conclusions were robust to decisions made during the review process such as inclusion criteria and imputing of missing data. Sensitivity analyses were also to be conducted to assess the influence of methodological quality.

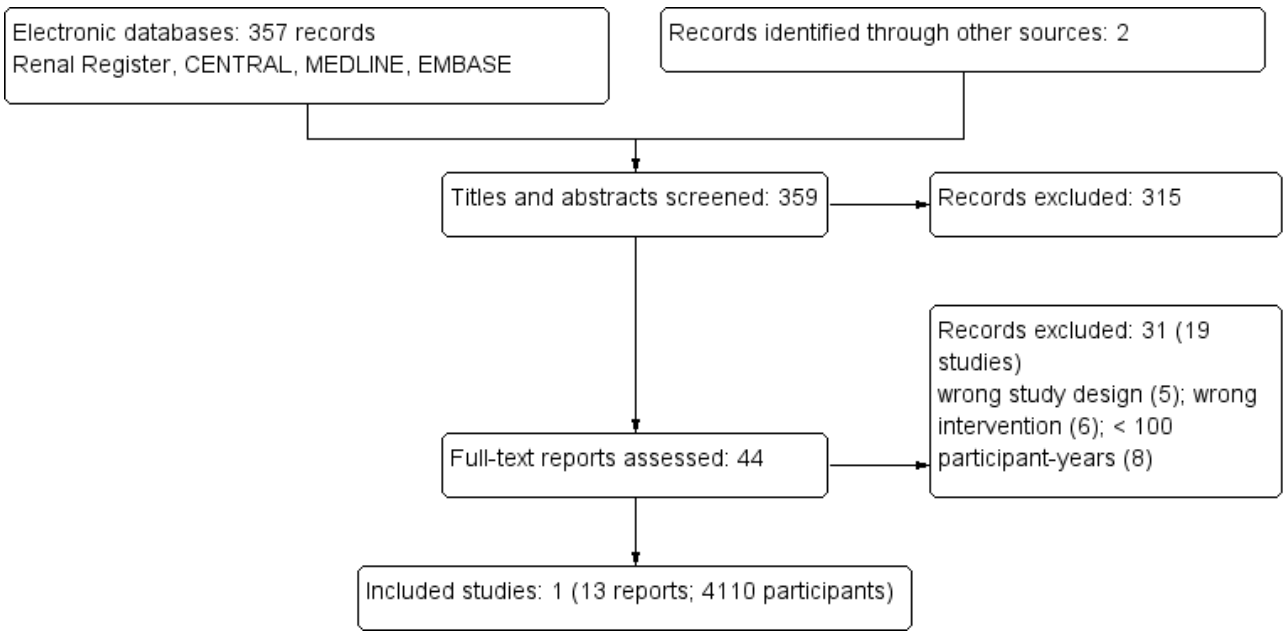
RESULTS

Description of studies

Results of the search

The literature search yielded a total of 359 records (Figure 1). Of these, 44 were reviewed in full text. One study (13 reports) was identified that met our inclusion criteria (FAVORIT Study 2006).

Figure 1. Study flow diagram



Included studies

Participants

The study randomised 4410 people aged 35 to 75 years with a functioning kidney transplant who were at least six months post-transplantation with stable kidney function and an elevated homocysteine level (≥ 11 µmol/L women; ≥ 12 µmol/L men). The mean follow-up time was 4.0 years.

Roughly one third (37.2%) were female, one quarter (23.5%) were of non-white race, one fifth had a history of cardiovascular disease (20.0%) and two fifths had diabetes mellitus (40.5%). Participants were recruited from the US (73%), Brazil (14.9%) and Canada (12.1%) between August 2002 and January 2007. The vast majority of participants would have been recruited during the era of mandatory grain fortification with folic acid which was introduced in 1998 in the USA and Canada (Crider 2011) and in June 2004 in Brazil (Orioli 2011). Patients had functioning transplants for an average of 5 ± 5.0 years standing with an average screening eGFR of 48.8 ± 16.2 mL/min. Mean homocysteine levels were 16.4 ± 1.3 mmol/L.

Interventions

The intervention was folic acid 5.0 mg plus high (50 mg vitamin B_6; 1.0 mg vitamin B_{12}) or low (1.3 mg vitamin B_6; 2.0 µg vitamin B_{12}) dose multivitamins.

Outcomes

The primary outcome was a composite of cardiovascular disease (cardiovascular death, MI, resuscitated sudden death, stroke, coronary artery revascularization, lower extremity revascularization, above-ankle amputation for severe arterial disease, carotid endarterectomy or angioplasty, abdominal aortic aneurysm repair or renal artery revascularization). Patients commencing dialysis continued on study treatment until they reached a primary endpoint whereupon study medication was ceased.

Excluded studies

After full text review we excluded 31 records (19 studies). The reasons for exclusion were: wrong study design (5); wrong intervention (6) or < 100 patient-years. See Characteristics of excluded studies.

Risk of bias in included studies

The identified study has an overall low risk of bias (Risk of bias in included studies).

Effects of interventions

Meta-analysis was not applied as only a single eligible study was identified (FAVORIT Study 2006).

FAVORIT Study 2006 found that, based on a subgroup of 143 participants, high dose folic acid and B group vitamins significantly lowered homocysteine levels (Analysis 1.1 (143 participants): -4.40 µmol/L, 95% CI -5.98 to -2.82).

Despite effectively lowering homocysteine levels there was no evidence the intervention impacted on any of the outcomes for this review.

- Cardiovascular mortality (Analysis 1.2 (4110 participants): RR 0.91, 95% CI 0.69 to 1.20)
- All-cause mortality (Analysis 1.3 (4110 participants): RR 1.04, 95% CI 0.88 to 1.22)
- MI (Analysis 1.4 (4110 participants): RR 1.02, 95% CI 0.77 to 1.35)
- Coronary revascularization (Analysis 1.5 (4110 participants): RR 0.93, 95% CI 0.73 to 1.19)
- Stroke (Analysis 1.6 (4110 participants): RR 1.08, 95% CI 0.69 to 1.71)
- Cerebrovascular revascularization (defined in the FAVORIT Study 2006 as carotid endarterectomy or angioplasty) (Analysis 1.7 (4110 participants): RR 1.11, 95% CI 0.45 to 2.73)
- Commencement of RRT (defined in the FAVORIT Study 2006 as dialysis-dependent kidney failure) (Analysis 1.8 (4110 participants): RR 1.12, 95% CI 0.91 to 1.37)
- Adverse gastrointestinal events (Analysis 1.9 (4110 participants): RR 1.06, 95% CI 0.83 to 1.36)
- All reported adverse events (Analysis 1.10 (4110 participants): RR 1.02, 95% CI 0.87 to 1.20).

No data were reported in the FAVORIT Study 2006 for change in kidney function, deep vein thrombosis and PE, lower limb amputation per se (although it was included in a PVD composite), adverse dermatological events, adverse neurological events or adverse malignant events.

There was no evidence the intervention impacted on the primary endpoint of the FAVORIT Study 2006, a cardiovascular event composite (RR 0.99, 95% CI 0.85 to 1.15), nor on any of the secondary endpoints not mentioned above including resuscitated sudden death (RR 0.80, 95% CI 0.32 to 2.02), PVD defined as lower extremity revascularization or amputation above the ankle for severe arterial disease (RR 1.17, 95% CI 0.81 to 1.67), abdominal aortic aneurysm repair (RR 0.60, 95% CI 0.14 to 2.50) and renal artery revascularization (RR 1.28, 95% CI 0.48 to 3.44).

DISCUSSION

Summary of main results

This review identified only one completed study that met our inclusion criteria for examining the effectiveness of homocysteine lowering in kidney transplant recipients. In this study, there was no evidence that homocysteine lowering had an effect on any of the assessed cardiovascular outcomes, including cardiovascular mortality, MI, and stroke, other clinical outcomes, including all-cause mortality, requirement for dialysis treatment or access thrombosis, nor on adverse effects.

Overall completeness and applicability of evidence

Beyond kidney transplantation, the impact of homocysteine has been studied in people with other categories of kidney disease. A systematic review performed by our group examined the impact of folic acid-based homocysteine lowering in people with any type of kidney disease categorised as ESKD, CKD and functioning kidney transplantation (Jardine 2012). Eleven studies were identified reporting 3045 cardiovascular events among 10,863 participants of which the FAVORIT Study 2006 contributed 4110 participants. There was no evidence homocysteine lowering reduced the primary cardiovascular composite endpoint either overall (RR 0.97, 95% CI 0.92 to 1.03) nor in any of three defined categories of kidney disease

(P = 0.785). This data is consistent with studies in the general population, where folic acid based homocysteine lowering has also not been found to prevent cardiovascular events in large RCTs. The B-Vitamin Treatment Trialists' Collaboration has performed two individual patient level data analyses of larger studies randomising participants to folate-containing B group vitamins (Clarke 2010; Vollset 2013) although neither were able to include the FAVORIT Study 2006. The first primarily analysed the impact on the incidence of vascular disease in 37,485 participants in eight studies while the second assessed cancer incidence in 49,621 participants in 13 studies. Over a median of five years of treatment, folate-containing B group vitamin supplementation had no impact on major vascular events (RR 1.01, 95% CI 0.97 to 1.05) or mortality (RR 1.02, 95% CI 0.97 to 1.08) despite an average 25% reduction in homocysteine levels. There was no evidence of heterogeneity in subgroup analyses comparing the impact of the intervention according to serum creatinine (< 80, 80 to 94 and ≥ 95 µmol/L). Similarly there was no impact on cancer incidence over average five years treatment duration (RR 1.06, 95% CI 0.99 to 1.13). In combination these studies appear to have effectively excluded any beneficial cardiovascular effect of homocysteine lowering therapy in the general population and in people with kidney disease.

Quality of the evidence

The included study (FAVORIT Study 2006) was of assessed as high quality.

Potential biases in the review process

We specifically included only RCTs with a minimum of 100 patient-years follow-up in our inclusion criteria to reduce the risk of reporting or publication bias that may be associated with small studies (Egger 1997). To investigate the impact of the 100 patient-year criteria on our results, we modified our inclusion criteria to include studies of any follow-up duration that met all other search criteria in a sensitivity analysis. Excluding the 100 patient-year minimum requirement resulted in identification of an extra six studies (Beaulieu 1999; Biagini 2002; Bostom 1997; Marcucci 2002; Perez 2004; Xu 2005a).The intervention used in these studies was either folic acid or folic acid, vitamin B_6 and vitamin B_{12}. Follow-up ranged from three to 30 patient-years. Baseline homocysteine levels ranged from 17 to 30 µmol/L (compared with levels of 100 to 400 µmol/L reported in classical homocysteinuria). Four studies found a significant decrease in fasting homocysteine levels with treatment compared with placebo/lower dose (Marcucci 2002, Beaulieu 1999, Xu 2005a, Bostom 1997). Perez 2004 compared standard and supraphysiological doses of folic acid, vitamin B_6 and vitamin B_{12} and found no significant difference in homocysteine levels between the groups. Some of these studies did not report baseline and achieved homocysteine levels for each group, which prevented their combination using meta-analysis (Bostom 1997; Perez 2004; Xu 2005a). Marcucci 2002 reported a significant decrease in carotid intima-media thickness (cIMT) in the treatment arm (0.95 ± 0.20 mm versus 0.64 ± 0.17 mm; P < 0.0001) and an increase in cIMT in the placebo group (0.71 ± 0.16 mm versus 0.87 ± 0.19 mm; P < 0.05). Xu 2005a found a significant increase in endothelium dependent and independent vasodilatation response following the intervention (12.2% ± 4.6% versus 8.8% ± 5.2%, t = 2.9, P < 0/01 and 17.6% ± 3.9% versus 12.2% ± 4.7%, t = 3.4, P < 0.01) and there were no significant changes observed in controls. None of these RCTs reported the defined clinical events and therefore could not contribute to our planned analyses. Therefore, regardless of the patient-year parameter in our inclusion criteria, we were unable to find more than one completed study that evaluated the effect of homocysteine lowering therapy on cardiovascular end points rather than surrogate markers for cardiovascular disease.

Agreements and disagreements with other studies or reviews

The KDIGO 2009 and CARI 2012 for the care of people with functioning kidney transplants do not comment on folic acid or B vitamin supplementation. The UK Renal Association suggests offering folic acid and B group vitamin supplementation to patients with kidney disease considered at risk of nutritional deficiency but notes insufficient evidence to recommend supraphysiological supplementation for vascular risk modification (The Renal Association 2010). The guidelines noted the (then) ongoing FAVORIT Study 2006 would supply evidence for people with functioning kidney transplants.

AUTHORS' CONCLUSIONS

Implications for practice

There is no current evidence to support the use of homocysteine lowering therapy for cardiovascular disease prevention in kidney transplant recipients.

Implications for research

Research focusing on mechanisms to reduce cardiovascular disease events in kidney transplant recipients is warranted.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

FAVORIT Study 2006

Methods	• Study design: parallel RCT • Duration of study: August 2002 to June 2009 • Duration of follow-up: mean follow-up 4.0 ± 1.5 years
Participants	• Country: Brazil, Canada, USA • Setting: 30 clinical sites • Inclusion criteria: 6 months or more post kidney transplantation; aged 35 to 75 years; CrCl ≥ 30 mL/min for participants recruited prior to July 2005, thence ≥ 30 mL/min (men) or 25 mL/min (women); homocysteine level ≥ 12.0 µmol/L (men) or ≥11.0 µmol/L (women); provision of informed consent; cognitive function adequate for patient to give accurate information; adequate transportation facilities; geographic accessibility for follow-up; within 120 days of screening • Number: treatment group (2056); control group (2054) • Mean age ± SD (years): treatment group (52 ± 9.4); control group (52 ± 9.5) • Sex (M/F): treatment group (1289/767); control group (1293/761) • Exclusion criteria: presence of cancer, end-stage congestive heart failure, liver, or pulmonary disease, progressive human immunodeficiency virus or other chronic wasting illness, which in the opinion of the study physician would limit the life expectancy of the patient to less than 2 years or prevent evaluation of recurrent or de novo CVD; other conditions that prevent reliable participation in the study (refractory depression, severe cognitive impairment, or alcoholism or other substance abuse); history of solid organ transplant other than the kidney or pancreas; pregnant or lactating women or women of childbearing potential not practicing birth control; < 3 months post–acute MI or stroke, or < 3 months post–coronary artery, renal artery, or lower extremity artery percutaneous transluminal coronary angioplasty, or lower extremity amputation; less than 6 months post–coronary artery bypass graft surgery, abdominal aortic aneurysm; participation in another clinical study specifically involving CVD risk factor management
Interventions	Treatment group

FAVORIT Study 2006 *(Continued)*

- High dose B group multivitamin
  - 5 mg folic acid
  - 50 mg vitamin B_6
  - 1mg vitamin B_{12}

Control group

- Low dose multivitamin
  - No folic acid
  - 1.4 mg vitamin B_6
  - 2.0 µg vitamin B_{12}

Other information

- Both vitamin preparations contained 1.5 mg vitamin B_1, 1.5 mg vitamin B_2, 60 mg vitamin C, 30 µg d-Biotin, 20 mg niacinamide and 10 mg pantothenic acid
- Participants continued on their intervention until study end or, in the case of those who developed dialysis-dependent ESKD, until the occurrence of their first primary endpoint

Outcomes	• Primary composite outcome: arteriosclerotic cardiovascular disease outcome (cardiovascular disease death, MI, resuscitated sudden death, stroke, coronary artery revascularization, lower extremity revascularization or, for severe arterial disease, amputation above the ankle, carotid endarterectomy or angioplasty, abdominal aortic aneurysm repair, or renal artery revascularization)
	• Secondary outcomes
	  ○ All-cause mortality
	  ○ Dialysis-dependent kidney failure
	  ○ Individual components of the primary outcome
	  ○ 'relevant' combinations of the components of the primary outcome

Funding source	• Government funded support: National Institute of Diabetes and Digestive and Kidney Diseases, the National Institutes of Health. The Office of Dietary Supplements, National Institutes of Health • Commercial: Manufacture of multivitamin preparations
Presence or absence of grain fortification	• Mandatory grain fortification status: mandatory fortification of grain was in place in the US, Canada for the duration of the study, and in Brazil from June 2004
Notes	• The study reports outcomes both according to intention-to-treat principles and outcomes censored 3 months after the return to dialysis. In this analysis, we have included the intention-to-treat outcomes. • The study was concluded after an interim analysis when the Data Safety and Monitoring Board recommended the study be concluded as it had 'conclusively answered its original hypothesis'.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization by permuted block, stratified by clinical site". Two different block sizes were used.
Allocation concealment (selection bias)	Low risk	"Randomization ... was performed through the data management system. Because the need for emergency unblinding was expected to be low, unblinding codes were stored securely at the Data Coordinating Center, accessible only to authorized staff."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This was a placebo-controlled RCT with both multivitamin preparations formulated to be similar in appearance and smell. Blinding was explicitly tested by survey of participants and study coordinators with 49% of each group providing incorrect guesses of intervention allocation.

FAVORIT Study 2006 *(Continued)*

		"The trial was a .. double blind, randomised clinical trial". "Both multivitamins [standard and low dose] were formulated to be similar in appearance and odor to facilitate blinding"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The first 4 components of the primary outcome (cardiovascular death, MI, resuscitated sudden death and stroke) were centrally reviewed and adjudicated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Completeness of follow-up: deceased (493); complete follow-up to June 2009 (2788); incomplete follow-up to June 2009 (822); no follow-up (7) Withdrawal of consent: treatment group (198/2056); control group (171/2054)
Selective reporting (reporting bias)	Low risk	Event data for all the primary and secondary outcomes according to intention-to-treat are reported.
Other bias	Low risk	No other biases detected

CrCl - creatinine clearance; ESKD - end-stage kidney disease; MI - myocardial infarction; RCT - randomised controlled trial

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

Study	Reason for exclusion
Ardalan 2003	Not RCT
Austen 2006	Cross-over study
Beaulieu 1999	< 100 patient-years. No clinical events, only plasma homocysteine levels
Biagini 2002	< 100 patient-years. No clinical events, only carotid intima-media thickness
Bostom 1997	< 100 patient-years. No clinical events, only plasma homocysteine levels
Bostom 2000	Not a comparison of homocysteine lowering
Jurewicz 2003	Not a comparison of homocysteine lowering
Juskowa 2006	Not a comparison of homocysteine lowering
LANDMARK 2 Study 2009	Not a comparison of homocysteine lowering
Lash 1998	Not a comparison of homocysteine lowering
Manrique 2005	< 100 patient-years
Marcucci 2002	< 100 patient-years. No clinical events, only carotid intima-media thickness
Nafar 2009	< 100 patient-years. This study has been terminated according to ClinicalTrials.gov information
Perez 2004	< 100 patient-years. No clinical events. Only clinical markers such as lipid profile
Rymarz 2009	Sequential or cross-over design
Savaj 2002	Not RCT

Study	Reason for exclusion
Shemin 2001	Not RCT
Teplan 2003b	Not homocysteine lowering (hypoenergetic hypolipidaemic diet and corticosteroids withdrawal)
Xu 2005a	< 100 patient-years. No clinical events. Only plasma homocysteine levels and endothelium dependent and independent vasodilation responses

DATA AND ANALYSES

Comparison 1. Folic acid-based homocysteine lowering versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Achieved change in homocysteine levels	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Cardiovascular mortality	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 All-cause mortality	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Myocardial infarction (fatal and non-fatal)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Coronary revascularization	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6 Stroke (fatal and non-fatal)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Cerebrovascular revascularization	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8 Commencement of renal replacement therapy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9 Adverse events: gastrointestinal	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10 All reported adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Folic acid-based homocysteine lowering versus control, Outcome 1 Achieved change in homocysteine levels.

Study or subgroup	Folic acid-based N	Folic acid-based Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
FAVORIT Study 2006	72	-4.6 (4.5)	71	-0.2 (5.1)		-4.4[-5.98,-2.82]

Favours folic acid-based -10 -5 0 5 10 Favours control

Analysis 1.2. Comparison 1 Folic acid-based homocysteine lowering versus control, Outcome 2 Cardiovascular mortality.

Study or subgroup	Folic acid-based n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
FAVORIT Study 2006	91/2056	100/2054		0.91[0.69,1.2]

Favours folic acid-based 0.5 0.7 1 1.5 2 Favours control

Analysis 1.3. Comparison 1 Folic acid-based homocysteine lowering versus control, Outcome 3 All-cause mortality.

Study or subgroup	Folic acid-based n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
FAVORIT Study 2006	251/2056	242/2054		1.04[0.88,1.22]

Favours folic acid-based 0.5 0.7 1 1.5 2 Favours control

Analysis 1.4. Comparison 1 Folic acid-based homocysteine lowering versus control, Outcome 4 Myocardial infarction (fatal and non-fatal).

Study or subgroup	Folic acid-based n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
FAVORIT Study 2006	96/2056	94/2054		1.02[0.77,1.35]

Favours folic acid-based 0.5 0.7 1 1.5 2 Favours control

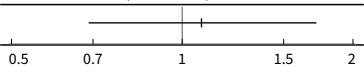
Analysis 1.5. Comparison 1 Folic acid-based homocysteine lowering versus control, Outcome 5 Coronary revascularization.

Study or subgroup	Folic acid-based n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
FAVORIT Study 2006	116/2056	124/2054		0.93[0.73,1.19]

Favours folic acid-based 0.5 0.7 1 1.5 2 Favours control

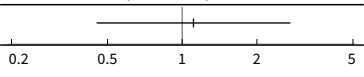
Analysis 1.6. Comparison 1 Folic acid-based homocysteine lowering versus control, Outcome 6 Stroke (fatal and non-fatal).

Study or subgroup	Folic acid-based n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
FAVORIT Study 2006	38/2056	35/2054		1.08[0.69,1.71]



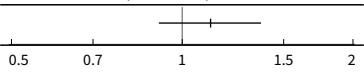
Analysis 1.7. Comparison 1 Folic acid-based homocysteine lowering versus control, Outcome 7 Cerebrovascular revascularization.

Study or subgroup	Folic acid-based n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
FAVORIT Study 2006	10/2056	9/2054		1.11[0.45,2.73]



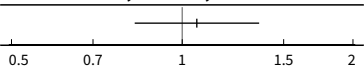
Analysis 1.8. Comparison 1 Folic acid-based homocysteine lowering versus control, Outcome 8 Commencement of renal replacement therapy.

Study or subgroup	Folic acid-based n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
FAVORIT Study 2006	181/2056	162/2054		1.12[0.91,1.37]



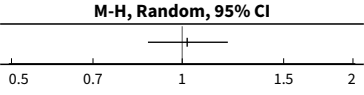
Analysis 1.9. Comparison 1 Folic acid-based homocysteine lowering versus control, Outcome 9 Adverse events: gastrointestinal.

Study or subgroup	Folic acid-based n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
FAVORIT Study 2006	121/2056	114/2054		1.06[0.83,1.36]



Analysis 1.10. Comparison 1 Folic acid-based homocysteine lowering versus control, Outcome 10 All reported adverse events.

Study or subgroup	Folic acid-based n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
FAVORIT Study 2006	269/2056	263/2054		1.02[0.87,1.2]



APPENDICES

Appendix 1. Electronic search strategies

Databases	Search terms
CENTRAL	1. MeSH descriptor: [Homocysteine] explode all trees 2. MeSH descriptor: [Hyperhomocysteinemia] this term only 3. homocysteine* in Trials 4. hyperhomocysteine* in Trials 5. #1 or #2 or #3 or #4 in Trials 6. MeSH descriptor: [Kidney Transplantation] this term only 7. kidney transplant*:ti,ab,kw (Word variations have been searched) 8. renal transplant*:ti,ab,kw (Word variations have been searched) 9. #6 and #7 and #8 10.#5 and #8
MEDLINE	1. Kidney Transplantation/ 2. exp Homocysteine/ 3. Hyperhomocysteinemia/ 4. hyperhomocystein$.tw. 5. homocystein$.tw. 6. or/2-5 7. and/1,6
EMBASE	1. exp kidney transplantation/ 2. Homocysteine/ 3. Hyperhomocysteinemia/ 4. hyperhomocysteine$.tw. 5. homocystein$.tw. 6. or/2-5 7. 7. and/1,6

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; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	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	*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; sequential-

(Continued)

Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	ly 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 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 standardized 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. subscales) 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

(Continued)

	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 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.

CONTRIBUTIONS OF AUTHORS

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

DECLARATIONS OF INTEREST

None stated

SOURCES OF SUPPORT

Internal sources

- The George Institute for Global Health, Australia.

  Dr Meg Jardine, Dr Sophie Zoungas, Dr Vlado Perkovic, Dr Alan Cass and Dr Martin Gallagher are employed by The George Institute for Global Health

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Kidney Transplantation; Cardiovascular Diseases [*mortality]; Cause of Death; Folic Acid [*administration & dosage]; Homocysteine [*blood]; Randomized Controlled Trials as Topic; Vitamin B Complex [*administration & dosage]

MeSH check words

Humans