

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

Interventions for lowering plasma homocysteine levels in dialysis patients (Review) Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

[Intervention Review]

Interventions for lowering plasma homocysteine levels in dialysis patients

Sagar U Nigwekar¹, Amy Kang^{2,3}, Sophia Zoungas⁴, Alan Cass^{3,5}, Martin P Gallagher³, Satyarth Kulshrestha⁶, Sankar D Navaneethan⁷, Vlado Perkovic³, Giovanni FM Strippoli^{8,9,10,11,12}, Meg J Jardine^{3,13}

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

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.

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

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 B₆, vitamin B₁₂) 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 B₆, vitamin B₁₂). 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.