Does folate therapy reduce the risk of coronary restenosis: an evidence-based report
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CRD summary
The authors concluded that the effect of folate on the coronary restenosis rate after balloon angioplasty differed between studies. Folate cannot be recommended for the treatment of coronary arterial disease until more research has been undertaken. The limited search and poor reporting of the review process make it difficult to assess the reliability of these conclusions.

Authors' objectives
To evaluate the effects of folate on the risk of coronary restenosis in patients with coronary arterial disease (CAD).

Searching
MEDLINE (via PubMed) and EMBASE were searched for studies reported in English, Dutch or German. Details of the search strategy were reported, but the search dates were not.

Study selection
Studies that evaluated the effect of folate on the risk of CAD in adults were eligible for inclusion. Studies that assessed cerebrovascular disease, peripheral vascular disease, renal disease, vascular endothelial function and homocysteine concentration were excluded.

The following details only apply to the three studies discussed in the review. The duration of follow-up was 7 or 42 months. Studies included patients who had undergone angioplasty with and without stenting and patients with stable CAD. One study assessed vascular events without further radiological examination.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Internal validity was assessed using the following criteria: study design, randomisation, sample size, placebo control, blinding, standardisation, stratification, duration of follow-up, losses to follow-up, intention-to-treat, ‘well defined domain and determinant’ and well-defined outcome. The studies were also graded using the hierarchy of study design described by Offringa.

The authors did not state how the validity assessment was performed.

Data extraction
For each study, relative risks (RRs) of coronary restenosis were presented with 95% confidence intervals (CIs).

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
The three studies scoring the highest points for internal validity were combined in a narrative. The results of a subgroup analysis in one study were reported separately for non-stented and stented lesions.

Results of the review
Five studies were eligible: three RCTs, one meta-analysis and one cohort study. Results from the three RCTs (n=1,434) were reported in the review.

Of these three RCTs, two were double-blinded and one was single-blinded, one used intention-to-treat analysis, and two
used a placebo control.

One study (205 patients undergoing coronary angioplasty) reported that folate was associated with a statistically significant reduction in the risk of coronary restenosis compared with placebo for patients with or without stenting: 19.6% versus 37.6% (RR 0.52, 95% CI: 0.32, 0.86, p=0.01).

The rate of restenosis was significantly lower for lesions without stent placement (101 lesions): 10.3% versus 41.9% (RR 0.25, 95% CI: 0.11, 0.57, p=0.001). There was no significant difference between folate and placebo for stented lesions: 20.6% versus 29.9% (p=0.32).

One RCT (636 patients undergoing coronary stenting) reported that folate was associated with an increase in the risk of restenosis (RR 1.30, 95% CI: 1.00, 1.69); the restenosis rate with folate was 8% higher than control (p=0.05).

One RCT (593 patients with stable CAD) reported no significant difference in the risk of vascular events between folate and placebo: 16.3% versus 19.1% (RR 0.85, 95% CI: 0.65, 2.87).

Authors' conclusions
The effects of folate on the coronary restenosis rate after balloon angioplasty differed between studies. Folate cannot be recommended for patients with CAD until more research has been undertaken.

CRD commentary
The review question was stated clearly. Inclusion criteria for the study design were broad, but results from only the three highest-quality studies were reported in the review; it was not clear if this decision was made post hoc or a priori. Restricting the search to publications in three specified languages listed in two databases raises the possibility of publication and language bias and might have resulted in the omission of other relevant studies. Study validity was assessed and the results reported. The methods used to conduct the review process were not described, so it is not known whether any efforts were made to reduce reviewer error and bias. It is not clear whether the studies used comparable doses of folate for treatment since the doses used were not reported. The narrative synthesis was appropriate given the differences between the studies. The evidence appears to support the authors’ conclusions, but the limited search and lack of reporting of the review process make it difficult to assess the reliability of these conclusions.

Implications of the review for practice and research
Practice: The authors stated that folate therapy cannot be recommended for patients with CAD until further research has been conducted.

Research: The authors did not state any implications for further research.

Funding
Not stated.

Bibliographic details

PubMedID
17612702

Original Paper URL

Indexing Status
Subject indexing assigned by NLM
MeSH
Coronary Restenosis /prevention & control; Folic Acid /therapeutic use; Homocysteine /blood; Vitamin B 12 /therapeutic use; Vitamin B 6 /therapeutic use

AccessionNumber
12007002959

Date bibliographic record published
09/08/2008

Date abstract record published
23/12/2008

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.