Does folate therapy reduce the risk of coronary restenosis?

An evidence-based report

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Background. **A high homocysteine level is associated with an increased risk of ischaemic heart disease. Folate therapy has shown to reduce the homocysteine blood level, but does it decrease the risk of coronary restenosis in patients with coronary arterial disease?**
Methods. **A systematic online literature search followed by a critical appraisal resulted in three suitable articles to provide an evidence-based evaluation of this clinical query.**
Results. **The rate of coronary restenosis was reduced after folate therapy, except in patients who have had coronary stenting. An adverse effect of folate therapy on in-stent coronary restenosis was observed.**
Conclusion. **The effects of folate therapy on the rate of coronary restenosis after balloon angioplasty are contradicting. Until more clinical research has been preformed we recommend a conservative attitude towards folate therapy. (*Neth Heart J* 2007;15:12-5.)**

Keywords: folic acid, treatment, homocysteine, coronary restenosis, coronary atherosclerosis

A Dutch general practice contains approximately 25 patients suffering from coronary heart disease, with an expected increase of up to 35 patients by the year 2015.[1] Besides elevated blood cholesterol level, diabetes, high blood pressure, age, the male gender, smoking and a family history of heart disease, hyperhomocysteinaemia is also considered to be an independent risk factor for cardiovascular disease.[2] Homocysteine is an amino acid in the blood. An elevated level of serum homocysteine (>12 µmol/l) is associated with an increased risk of ischaemic heart disease, stroke and peripheral vascular disease.[3] A daily intake of at least 0.5 mg vitamin B12 and folic acid has shown to reduce the plasma homocysteine concentrations by 25 to 30%.[4] However, it remains to be elucidated whether folate therapy is beneficial in the prevention of mortality and morbidity due to arteriosclerosis. Until now, no controlled treatment studies have been able to demonstrate that folate therapy reduces the risk of developing atherosclerosis or affects the development or recurrence of cardiovascular disease. Although treatment with folic acid and vitamin B12 is a relatively simple and cheap method to reduce serum homocysteine with little to no side effects, evidence for the benefit of lowering homocysteine levels is lacking and therefore no guidelines on this topic have been set up.[5]

Our clinical query in this study was: Does folate therapy decrease the risk of coronary restenosis in patients suffering from coronary arterial disease (CAD)?

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Methods

Search strategy

To obtain relevant literature, online databases were consulted using the PubMed and Embase search engines. Medline was explored on title and abstract using keywords sought in the index, and specified by a sensitive broad search with therapy chosen as clinical study category in clinical queries. In Embase EMTREE keywords were attained to search on title and abstract within the disease search form, for all years, with therapy chosen as link. These findings were combined into adequate search strings with use of the Boolean operator 'OR' and 'AND' (table 1), resulting in 504 articles. After screening all articles upon our set of inclusion and exclusion criteria, only 20 articles remained. The inclusion criteria handled were risk of CAD after lowered homocysteine concentration by folate therapy as outcome measure, written in English, Dutch or German. The exclusion criteria were cerebro-

Table 1. Literature search.

Online database	Search string	Articles
PubMed	((“folate”[Title/Abstract] OR “vitamin b”[Title/Abstract] OR “folic acid”[Title/Abstract]) AND (“homocysteine”[Title/Abstract]) AND (“coronary”[Title/Abstract])) AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])	122
Embase only	‘homocysteine’/dm_th AND (‘vitamin b group’/dm_th OR ‘folic acid’/dm_th) AND ‘ischemic heart disease’/dm_th AND [embase]/lim	382

vascular disease, peripheral arterial disease, renal disease, children, vascular endothelial function as outcome measure or homocysteine concentration after folate therapy as outcome measure. After excluding double and unavailable articles, 12 relevant articles remained. When viewing their full text, another seven articles were left out. Twice, three articles originated from the same study group, as one was the pilot study, the second the main study and the last the extended follow-up of the main study. Comparing results of identical study populations possibly affects the objectivity of our conclusion. Therefore, only one article from each study group was selected, according to the most relevant outcome measure[6] and the longest follow-up,[7] respectively. Further, three articles were an annotation on one and/or two of the five final remaining articles, Schnyder et al.[6] and Liem et al.[7] and do not supply appropriate data for answering our clinical query.

Critical appraisal

The five selected articles were read carefully. Each study was evaluated on internal validity and relevancy by means of a checklist as shown in tables 2 and 3. Several items were graded on a five-point scale ranging from

Table 2. Internal validity.

Articles	Study design	Randomisation	Population size	Use of placebo	Blinding	Standardisation	Stratification	Length follow-up (months)	Loss to follow-up	Intention to treat	Well-defined domain	Well-defined determinant	Well-defined outcome	Level of evidence	Ranking
Schnyder[6]	PRCT	++	205	Yes	Yes (2)	++	++	7	28	No	++	++	++	1b	1
Lange[9]	MC-RCT	++	636	Yes	Yes (2)	++	++	7	91	No	+	++	++	1b	2
Liem[7]	RCT	++	593	No	Yes (1)	++	++	42	0	Yes	++	++	++	1b	3
Boushey[10]	MA	—	2955	No	No	+	—	?	?	No	±	++	-	2a	4
Anderson[11]	LCS	-	2481	No	No	+	+	24	?	No	±	±	-	3	5

Very poor=—, poor=-, moderate=±, good=+, excellent=++, not mentioned=?, MA=meta-analysis, RCT=randomised controlled trial, PRCT=prospective RCT, MC-RCT=multicentre RCT, LCS=longitudinal cohort study, 1=single blinded, 2=double blinded, 1b=RCT of good quality, 2a=systematic review of cohort or patient-control studies with consistency of separate results, 3=poor quality patient series or cohort or patient-control studies.

Table 3. Relevancy.

Articles	Relevancy research question	Relevancy domain	Relevancy determinant	Relevancy outcome	Level of relevance	Ranking
Schnyder[6]	++	++	++	++	++	1
Lange[9]	+	+	++	++	+	2
Liem[7]	±	+	+	±	±	3
Boushey[10]	±	-	+	+	±	4
Anderson[11]	±	±	-	-	-	5

Very poor=—, poor=-, moderate=±, good=+, excellent=++.

Table 4. Results.

Coronary restenosis	Schnyder et al.[6]	Lange et al.[9]	Liem et al.[7]
RR (95% CI)	0.52 (0.32-0.86)	1.30 (1.00-1.69)	0.85 (0.65-2.87)
RRR	48%	-	-
RR (95% CI) non-stented lesions	0.25 (0.11-0.57)	-	-
RRR non-stented lesions	76%	-	-
RR (95% CI) stented lesions	0.69 (0.38-1.27)	-	-
RRR stented lesions	31%	-	-

RR=relative risk, 95% CI=95% confidence intervals, RRR=relative risk reduction.

very poor to excellent. Furthermore, a level of evidence was added according to criteria described by Offringa,[8] which was based on the appraised internal validity. After evaluation, all articles were ranked according to the appraised level of evidence and relevance. Finally, the results of the top three articles (table 4) were assessed to provide an evidence-based estimated answer on this query.

Results

Schnyder et al.[6] studied the effect of lowering plasma homocysteine levels on restenosis after coronary angioplasty in 205 patients who had undergone angioplasty with or without stenting of at least one coronary stenosis of ≥50%. They were randomly assigned to folate treatment or placebo. The two groups did not differ in sex, age, cardiovascular risk factors, use of statins or antihypertensive drugs. Total plasma homocysteine levels and coronary angiograms were attained at baseline and again at six months' follow-up. Both the patients and cardiologist were blinded for treatment and homocysteine levels.

After approximately seven months, 19.6% (18 of 92 patients) of the group treated with folate had coronary restenosis, compared with 37.6% (32 of 85 patients) in the control group (p=0.01). The decrease in homocysteine levels was greater in patients without restenosis than in patients with restenosis (relative risk reduction 26.6 vs. 12.5%; p=0.038). When considering 101 individual coronary stenotic lesions after balloon angioplasty without stent placement, a significantly lower rate of restenosis was observed in the folate group (10.3%; 6 of 58 lesions) than in the placebo group (41.9%; 18 of 43 lesions) (p<0.001). However, evaluation of 130 stented lesions showed a smaller difference between the numbers of restenosis in treated patients (20.6%; 13 of 63 lesions) versus the controls (29.9%; 20 of 67 lesions; p=0.32).

Lange et al.[9] tested the effect of folate therapy on the risk of angiographic restenosis after coronary stent placement in a double-blind, multicentre, randomised, placebo-controlled trial. A total of 636 patients awaiting coronary stenting, were enrolled. Demographic and clinical characteristics, including the use of statins, diabetic and antihypertensive drugs, and laboratory findings were equally distributed between the patients receiving folate and the controls. Plasma levels of homocysteine were obtained before and six months after the procedure. Coronary angiograms were made at baseline, immediately after stenting, and at follow-up. Although homocysteine levels dropped with folate therapy (9.0 µmol/l; p<0.001), the coronary luminal diameter significantly decreased (1.59 mm vs. 1.74 mm; p=0.008) instead of increasing. The rate of restenosis was 8% higher (p=0.05) with six months of folate therapy than without, implying an adverse effect of folate treatment on the risk of restenosis among patients who have received a coronary stent.

Liem et al.[7] included 593 patients with stable CAD to study the cardiovascular mortality and morbidity when treated with folic acid. After having randomly assigned 300 patients to receive open-label folic acid and 293 patients to standard care, serving as controls, they were followed up for a maximum of five years. Both study groups were similar in terms of sex, age, cardiovascular risk factors and the use of statin therapy. During the entire study clinical events were carefully registered. Laboratory examinations were planned at three, six, and 12 months and every six months thereafter to measure homocysteine blood concentrations. The homocysteine blood concentrations decreased by 18% in patients treated with folic acid, whereas the homocysteine blood concentrations in the controls remained the same. At the end of the follow-up, 49 (16.3%) vascular events in the folic acid group and 56 (19.1%) in the control group were observed, showing no significant clinical benefit of folic acid intervention.

Discussion

Schnyder et al.[6] provide evidence that a plasma homocysteine level lowered by folate therapy significantly reduces the rate of restenosis after coronary angioplasty without stent placement. However, this effect was not observed in the stented coronary arteries. A similar trend was observed by Lange et al.[9] showing a statistically significantly increased rate of in-stent

restenosis in patients treated with folate compared with those receiving a placebo. At the same time, no higher incidence of death or infarction was found in the folate-treated group, indicating that folate therapy for prevention of CAD has no life-threatening consequences. The observed difference in outcome between balloon angioplasty and stenting might correspond to a difference in the vascular wall mechanisms of restenosis. After coronary stenting, restenosis is primarily due to proliferation of the tunica media, while after balloon angioplasty thrombus formation plays the predominant role in restenosis. The latter is probably more susceptible to the folate-induced effects of homocysteine decrement.

Liem et al.[7] only documented the vascular events occurring in patients diagnosed with stable CAD during a period of five years without further radiological examination, thus lacking an exact measure of the degree of restenosis in the coronaries. Nevertheless, a primary endpoint containing recurrent fatal or nonfatal myocardial infarction and invasive coronary procedures, such as percutaneous coronary intervention and coronary-artery bypass grafting, does provide an indication of the extent of cardiovascular atherosclerotic risk. However, Liem et al.[7] were unable to find any evident change in the number of experienced cardiovascular events between using folic acid and not. A possible explanation for the absence of effect could be that their whole population was at a reduced risk of vascular complications, considering the fact that at entry most patients had already been on statin treatment for several years. Therefore the additional contribution of folate therapy to the standard care against atherosclerotic progression is disputable.

Conclusion

The registered effects of folate therapy on the rate of coronary restenosis after balloon angioplasty are contradicting. The noted beneficial effect of folate intake on the rate of restenosis in nonstented coronary arteries could not be observed in stented coronary arteries, where it even seemed to have an adverse effect. Adding folate therapy to the current treatment of patients at risk for myocardial ischaemia lacks scientific support. Therefore, we recommend maintaining the standard medical care for patients with CAD applied nowadays and uphold a conservative attitude towards folate therapy until more clinical research has been performed. ■

References

1 Volksgezondheid Toekomst Verkenning 1997. De som der delen. Rwaard D, Kramers PGN (ed) Amsterdam: *Elsevier/De Tijdstroom*, 1997.
2 Tervahauta M, Pekkanen J, Nissinen A. Risk factors of coronary heart disease and total mortality among men with and without preexisting coronary heart disease. Finnish cohorts of the Seven Countries Study. *J Am Coll Cardiol* 1995;**261**:623-9.
3 Epstein FH. Homocysteine and atherothrombosis. *NEJM* 1998; **338**:1042-50.
4 Homocysteine Lowering Trialists' Collaboration. Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomised trials. *BMJ* 1998;**316**:894-8.
5 Graham I, Meleady R. Heart attacks and homocysteine. Time for a randomised controlled trial of plasma homocysteine reduction. *BMJ* 1996;**313**:1419-20.
6 Schnyder G, Roffi M, Pin R, et al. Decreased rate of coronary restenosis after lowering of plasma homocysteine levels. *NEJM* 2001;**345**:1593-600.
7 Liem A, Reynierse-Buitenwerf GH, Zwinderman AH, et al. Secondary prevention with folic acid: Results of the Goes extension study. *Heart* 2005;**91**:1213-4.
8 Offringa M, Assendelft WJJ, Scholten RJPM. Inleiding in evidence based medicine; Klinisch handelen gebaseerd op bewijsmateriaal. Bohn Stafleu van Loghum, 2nd edition 2003.
9 Lange H, Suryapranata H, De Luca G, et al. Folate therapy and in-stent restenosis after coronary stenting. *NEJM* 2004;**350**:2673-81.
10 Boushey CJ, Beresford SAA, Omenn GS, et al. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. *JAMA* 1995;**274**:1049-57.
11 Anderson JL, Jensen KR, Carlquist JF, et al. Effect of folic acid fortification of food on homocysteine-related mortality. *Am J Med* 2004;**1**:158-64.