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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Is folic acid supplementation useful for chronic kidney disease?

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Abstract

Patients with chronic kidney disease have higher cardiovascular risk than general population, a fact that has been linked to high homocysteine levels. Folic acid supplementation can reduce homocysteine levels, which would reduce cardiovascular events. However, there is controversy about the clinical effects of this measure. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified six systematic reviews comprising 13 trials addressing the question of this article. We combined the evidence using meta-analysis and generated a summary of findings following the GRADE approach. We concluded folic acid supplementation does not reduce the risk of myocardial infarction or stroke in patients with chronic kidney disease, and might have no effect on mortality.

Problem

It is clearly established patients with chronic kidney disease have a higher cardiovascular risk than the general population. However, despite control of classical risk factors (diabetes, hypertension, dyslipidemia, and smoking, among others) there is still a difference compared to population with these conditions without chronic kidney disease. In parallel, it has been found homocysteine levels are elevated in chronic kidney disease and there is an association with cardiovascular events and consequent mortality.

Considering folic acid can reduce homocysteine levels, it has been proposed as a potentially effective treatment to reduce cardiovascular diseases in patients with chronic kidney disease. However, there is controversy about the clinical effects of this measure.

Methods

We used Epistemonikos database, which is maintained by screening more than 30 databases, to identify systematic reviews and their included primary studies. With this information, we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages

- Folic acid supplementation does not reduce the risk of acute myocardial infarction or stroke in patients with chronic kidney disease.
- Folic acid supplementation might have no effect on mortality in patients with chronic kidney disease, but the certainty of the evidence is low.
- The most rigorous and updated systematic reviews agree it is unlikely folic acid supplementation can have a beneficial effect in chronic kidney disease.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found six systematic reviews [1],[2],[3],[4],[5],[6]including 13 randomized controlled trials reported in 24 references [7],[8],[9],[10],[11],[12],[13],[14],[15],[16],[17],[18],[19],[20],[21], [22],[23],[24],[25],[26],[27], [28],[29],[30],[31],[32].
What types of patients were included	General characteristics: The average age of patients in the trials was 58.7 years. The average percentage of men was 66%. Type and stage of kidney disease: Three trials [23],[30],[32] included patients on any stage of chronic kidney disease, four trials [7],[24],[27],[29] on pre-dialysis stage, five on dialysis [22],[25],[26],[28],[31]and one after transplantation [9]. Ten trials [9],[22],[23],[25],[26],[27],[28],[29],[31],[32] included any type of kidney disease, two trials [7],[30] included only diabetic nephropathy and one trial [24] included diabetic nephropathy or vascular nephropathy. Comorbidities: The average percentage of patients with a history of acute myocardial infarction was 40.9%, including one trial that restricted inclusion to post-infarction patients [27]. The average percentage of patients with diabetes was 40.9%, with two trials using this as an inclusion criterion [7],[30].
What types of interventions were included	Five trials [25],[28],[30],[31],[32] evaluated folic acid as monotherapy, and eight trials [7],[9],[22],[23],[24],[26],[27],[29] in combination with vitamin B6 and/or B12. The average dose of folic acid was 8.8 mg/day, ranging from 2 to 40 mg/day. Eight trials [7],[23],[24],[27],[28],[29],[30],[32] compared against placebo, two trials [25],[26] compared against usual care, one trial [9] against vitamin B and two trials [22],[31] against a lower dose of folic acid with or without vitamin B supplement.
What types of outcomes were measured	The different systematic reviews identified grouped the outcomes as follows: • General mortality • Cardiovascular mortality • Acute myocardial infarction • Stroke • Change on homocysteine levels • Incidence of any cardiovascular event • Incidence of major cardiovascular events • Progression of nephropathy • Adverse effects

Summary of findings

The information on the effects of folic acid in patients with chronic kidney disease is based on thirteen randomized trials involving 11,049 patients.
Nine trials (8,500 patients) measured the outcome mortality [7],[9],[22],[23],[24],[26],[28],[31],[32], seven trials (7,718 patients) measured myocardial infarction [7],[9],[22],[23],[26],[31],[32] and seven trials (8,536 patients) measured stroke [9],[22],[23],[24],[26],[31],[32].

The summary of findings is the following:

- Folic acid supplementation might have no effect on mortality in patients with chronic kidney disease, but the certainty of the evidence is low.
- Folic acid supplementation does not reduce the risk of acute myocardial infarction or stroke in patients with chronic kidney disease. The certainty of the evidence is high.

Folic acid for chronic kidney disease

Patients Chronic kidney disease
Intervention Folic acid
Comparison Placebo

Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT folic acid	WITH folic acid		
	Difference: patients per 1000			
Mortality	237 Per 1000	176 per 1000	RR 0.74 (0.54 to 1.01)	⊕⊕◯◯ Low[1,2]
	Difference: 61 patients less per 1000 (Margin of error: 109 less to 2 more)			
Acute myocardial infarction	77 per 1000	74 per 1000	RR 0.96 (0.82 to 1.13)	⊕⊕⊕⊕ High
	Difference: 3 patients less per 1000 (Margin of error: 14 less to 10 more)			
Stroke	28 per 1000	27 per 1000	RR 0.99 (0.76 to 1.29)	⊕⊕⊕⊕ High
	Difference: 1 patient less per 1000 (Margin of error: 7 less to 7 more)			

RR= Risk ratio.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article)

* The risk **WITHOUT folic acid** is based on the risk in the control group of the trials. The risk **WITH folic acid** (and its margin of error) is calculated from relative effect (and its margin of error)

[1] The certainty of the evidence was downgraded in one level for inconsistency because the results for this outcome differ substantially across the different trials.
[2] The certainty of the evidence was downgraded in one level for imprecision because the confidence interval includes the possibility of a beneficial effect.

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.
† Substantially different = a large enough difference that it might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply

- The evidence presented in this summary applies to all patients with chronic kidney disease, regardless of etiology, stage or comorbidities.

About the outcomes included in this summary

- The outcomes included in this summary are those considered critical for decision-making by the authors. They are generally in line with those mentioned by the systematic reviews identified and the main guidelines.
- We favored general mortality over cardiovascular mortality, because cause-specific outomes are less informative for patients. However, the inclusion of cardiovascular mortality does not lead to different conclusions.
- Folic acid effect is supposed to be mediated by the reduction of cardiovascular events. However, some authors have proposed a mechanism through reduction of progression of chronic kidney disease. So, it would be important to have more accurate information on total mortality, and eventually progression of kidney disease, for which there is little information on current studies

Balance between benefits and risks, and certainty of the evidence

- This is an intervention that probably leads to no benefit, so although it has minimal side effects, the risk/benefit balance is unfavorable

What would patients and their doctors think about this intervention

- Most patients and their doctors faced with this decision should be against its use.
- However, it is likely that some patients or doctors placing greater value on the low probability of a benefit might be inclined to support its use, especially as there is no consensus among the different clinical guidelines.

Resource considerations

- It is a relatively low-cost intervention, so probably this factor is not determinant for decision-making.

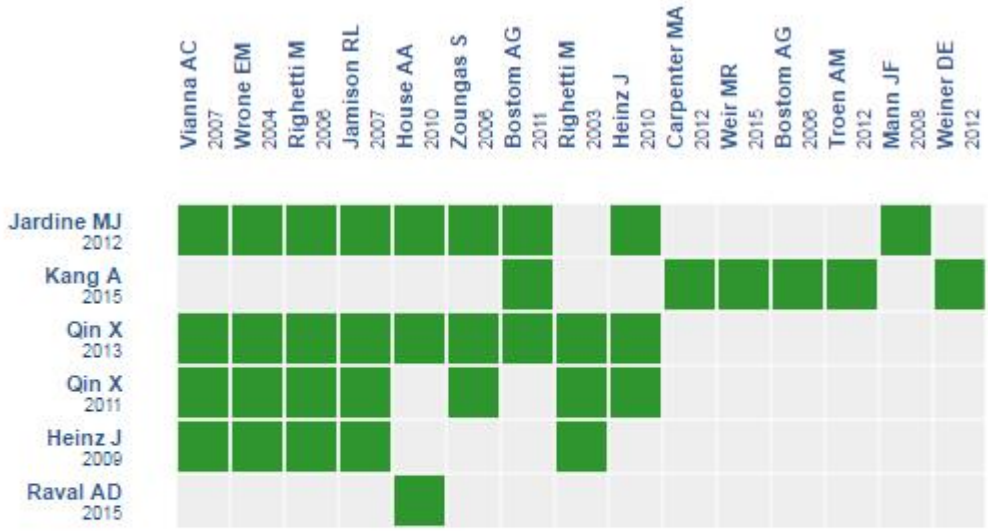
Differences between this summary and other sources

- There are discrepancies between the systematic reviews identified. Our summary agrees with the newest, which are also more complete and rigorous [1],[2],[6]
- The main guidelines, as the KDIGO [33], National Kidney Foundation (KDOQI) [34], and Canadian Society of Nephrology [35] do not mention folic acid as part of the management of patients with chronic kidney disease.

Could this evidence change in the future?

- The probability that future evidence changes the conclusions of this summary is very low for cardiovascular events, although it could change what we know about total mortality, or other outcomes.
- There is at least one published trial not included in any of the identified reviews [36] that could provide relevant information.
- We did not identify ongoing trials on the International Clinical Trials Registry Platform of the World Health Organization.

How we conducted this summary
Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version:** Folic acid for chronic kidney disease.

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

The details about the methods used to produce these summaries are described here http://dx.doi.org/10.5867/medwave.2014.06.5997.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

These summaries follow a rigorous process of internal peer review.

Conflicts of interest
The authors do not have relevant interests to declare.

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