Supplementary Table 1. Risk-of-bias assessment of included trials

Trial	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other potential bias
ASFAST (2006)[30], Australia and New Zealand	Unclear risk Quote: patients who met the entry criteria were randomly assigned Comment: insufficient information about the sequence generation process	Unclear risk Comment: insufficient information	Low risk Quote: doubleblind randomized study Comment: probably done	Low risk Quote: doubleblind randomized study Comment: probably done	Low risk Comment: no patients lost follow-up	Low risk Comment: study protocol is available, and all of the study's prespecified outcomes of interest in the review have been reported in the prespecified way	Low risk Comment: study seems to be free of other sources of bias
CSPPT (2015)[10], China	Low risk Quote: randomization was performed centrally by means of 4 randomization tables: 1wasa randomiza tion of drug code and treatment allocation, and the other 3 were *MTHFR ' C677T* genotype–specific randomized sequences with a fixed block size of 4 Comment: probably done	Low risk Quote: randomization was performed centrally by means of 4 randomization tables Comment: probably done	Low risk Quote: all study investigators and participants were blinded to the randomization procedure and the treatment assignments Comment: probably done	Low risk Quote: double blind clinical trial Comment: probably done	Low risk Comment: 0.3% vs. 0.3% patients lost follow-up	Low risk Comment: study protocol is available, and all of the study's prespecified outcomes of interest in the review have been reported in the prespecified way	Low risk Comment: study seems to be free of other sources of bias
Heinz et al. (2010)[34], Germany	Unclear risk Quote: patients were randomized to 2 treatment groups Comment: insufficient information about the sequence generation process	Low risk Quote: the code numbers were kept within the central pharmacy of the university hospital Comment: probably done	Low risk Quote: all study investigators staff, and participants were blinded to the randomization procedure and treatment assignments Comment: probably done	Low risk Quote: doubleblind, placebocontrolled, randomized multicenter trial Comment: probably done	Low risk Comment: no patients lost follow-up except withdrew consent	Low risk Comment: study protocol is not available, but the published reports clearly include all expected outcomes, including those that were prespecified	Low risk Comment: study seems to be free of other sources of bias
Kotwal et al. (2015)[11], India	Low risk Quote: randomization was done by generating pseudo numbers by scientific calculator Comment: probably done	Unclear risk Comment: insufficient information	Low risk Quote: the participants, principal investigator as well as those involved with data analysis were unaware of the subject allocation arms Comment: probably done	Low risk Quote: coworkers were included from the local areas for appropriate randomized allocation and follow up Comment: probably done	Low risk Comment: no patients lost follow-up	Unclear risk Comment: study protocol is not available, insufficient information to permit judgement	Low risk Comment: study seems to be free of other sources of bias
Liem et al. (2004)[26], Netherlands	Unclear risk Quote: patients were randomized to treatment Comment: insufficient information about the sequence generation process	Unclear risk Comment: insufficient information	High risk Quote: open-label	High risk Quote: open-label	Low risk Comment: no patients lost follow-up	Low risk Comment: study protocol is not available, but the published reports clearly include all expected outcomes, including those that were prespecified	Unclear risk Comment: insufficient information

Supplementary Table 1. Continued

Trial	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other potential bias
Liem et al. (2005)[27], Netherlands	Low risk Quote: a computer program randomly allocated patients Comment: probably done	Low risk Quote: a computer program randomly allocated patients Comment: probably done	High risk Quote: open-label	High risk Quote: open-label	Low risk Comment: no patients lost follow-up	Low risk Comment: study protocol is not available, but the published reports clearly include all expected outcomes, including those that were prespecified	Low risk Comment: study seems to be free of other sources of bias
Mark et al. (1996)[25], China	Low risk Quote: randomization was performed in blocks of 10 patients within strata defined by commune, gender, and age Comment: probably done	Unclear risk Comment: insufficient information	Unclear risk Comment: insufficient information	Unclear risk Comment: insufficient information	Low risk Comment: no patients lost follow-up	Low risk Comment: study protocol is not available, but the published reports clearly include all expected outcomes, including those that were prespecified	Low risk Comment: study seems to be free of other sources of bias
NORVIT (2006)[28], Norway	Low risk Quote: the randomization was performed in blocks of 20 by Alpharma Comment: probably done	Low risk Quote: the randomization was performed in blocks of 20 by Alpharma Comment: probably done	Low risk Quote: all study personnel and participants were unaware of the treatment assignments Comment: probably done	Low risk Quote: doubleblind Comment: probably done	Low risk Comment: no patients lost follow-up except withdrew consent or stop taking study medication	Low risk Comment: study protocol is not available, but the published reports clearly include all expected outcomes, including those that were prespecified	Low risk Comment: study seems to be free of other sources of bias
Righetti et al. (2006)[29], Italy	Unclear risk Quote: an independent person performed randomization for treatment using a box containing blind numbers Comment: insufficient information about the sequence generation process	Unclear risk Comment: insufficient information	High risk A single-center, open, prospective trial	High risk A singlecenter, open, prospective trial	Low risk Comment: no patients lost follow-up except withdrew consent or stop taking study medication	Low risk Comment: study protocol is not available, but the published reports clearly include all expected outcomes, including those that were prespecified	Low risk Comment: study seems to be free of other sources of bias
SEARCH (2010)[35], UK	Low risk Quote: the central telephone randomization system Comment: probably done	Low risk Quote: the central telephone randomization system Comment: probably done	Low risk Quote: doubleblind randomized controlled trial Comment: probably done	Low risk Quote: doubleblind randomized controlled trial Comment: probably done	Low risk Comment: no patients lost follow-up	Low risk Comment: study protocol is available, and all of the study's prespecified outcomes of interest in the review have been reported in the prespecified way	Low risk Comment: study seems to be free of other sources of bias

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Supplementary Table 1. Continued

Trial	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other potential bias
SU.FOL.OM3 (2010)[32], France	Low risk Quote: randomization was performed by means of a computerized block sequence Comment: probably done	Low risk Quote: the allocation of participants was programmed by the statistical coordinating centre Comment: probably done	Low risk Quote: patients, clinicians, trial coordinators, and outcome investigators were blinded to treatment allocation Comment: probably done	Low risk Quote: double blind, randomised, placebo controlled trial Comment: probably done	Low risk Comment: <1% participants lost to follow-up except withdrew consent	Low risk Comment: study protocol is available, and all of the study's prespecified outcomes of interest in the review have been reported in the prespecified way	Low risk Comment: study seems to be free of other sources of bias
VITATOPS (2010)[33], Multicountries	Low risk Quote: patients were randomly allocated by means of a central 24-h telephone service or an interactive website Comment: probably done	Low risk Quote: allocation was by use of random permuted blocks stratified by hospital Comment: probably done	Low risk Quote: patients, clinicians, trial coordinators, and outcome investigators were masked to treatment allocation Comment: probably done	Low risk Quote: a randomised, double-blind, parallel, placebocontrolled trial Comment: probably done	Low risk Comment: the rate of loss to final follow-up was 8.7% vs. 8.5%	Low risk Comment: study protocol is available, and all of the study's prespecified outcomes of interest in the review have been reported in the prespecified way	Low risk Comment: study seems to be free of other sources of bias
WENBIT (2008)[31], Norway	Low risk Quote: the randomization sequence was generated in blocks of 20 by Alpharma Inc Comment: probably done	Low risk Quote: the randomization code was kept at Alpharma Inc until data entry was completed Comment: probably done	Low risk Quote: participants, study and laboratory personnel, and the steering and endpoints committees were unaware of the treatment allocation Comment: probably done	Low risk Quote: doubleblind Comment: probably done	Low risk Comment: no patients lost follow-up except withdrew consent	Low risk Comment: study protocol is not available, but the published reports clearly include all expected outcomes, including those that were prespecified	Low risk Comment: study seems to be free of other sources of bias

ASFAST, Atherosclerosis and Folic Acid Supplementation Trial; CSPPT, China Stroke Primary Prevention Trial; NORVIT, Norwegian Vitamin; SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; SU.FOL.OM3, SUpplementation with FOlate, vitamin B6 and B12 and/or OMega-3 fatty acids; VITATOPS, VITAmins TO Prevent Stroke; WENBIT, Western Norway B-Vitamin Intervention Trial.