Vitamin C for treating atrial fibrillation (Review)

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[Intervention Review]

Vitamin C for treating atrial fibrillation

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ABSTRACT

Background

Atrial fibrillation (AF) is the most common sustained arrhythmia and contributes substantially to cardiac morbidity. AF is associated with oxidative stress and therefore vitamin C as a known antioxidant might influence AF.

Objectives

To assess the efficacy of vitamin C for the secondary prevention of AF and for treating AF.

Search methods

We searched CENTRAL, MEDLINE, EMBASE on 23 March 2015. In addition, we searched clinical trial registers and checked reference lists of relevant papers as well as contacted authors of relevant studies for ongoing and unpublished trials.

Selection criteria

Randomised trials on vitamin C that measured AF as an outcome.

Data collection and analysis

Two review authors independently read the trial reports and extracted data.

Main results

We identified 14 trials about secondary prevention of AF in high-risk patients. Thirteen trials (N = 1641) contributed to our meta-analyses. Twelve trials examined post-operative AF (POAF) in cardiac surgery patients and one trial examined the recurrence of AF in cardioversion patients. We found no trials about treating persistent or permanent AF.

Vitamin C decreased the incidence of POAF by 34% (95% CI 23% to 43%; participants = 1597; studies = 12; I^2 = 49%; moderate quality of evidence). The Number Needed to Treat to Benefit (NNTB) ranged from 4.2 to 6.6 in the six studies in which vitamin C significantly decreased POAF. In the cardiac surgery studies, vitamin C decreased the length of hospital stay by 11.4% (95% CI 7.6% to 15.2%; participants = 1399; studies = 9; I^2 = 31%; moderate quality of evidence). The absolute duration of hospital stay was shortened by 0.73 days (95% CI 0.45 to 1.00 days; participants = 1399; studies = 9; I^2 = 57%; moderate quality of evidence). One study in Greece examined the effect of vitamin C on AF patients after their successful cardioversion. Vitamin C decreased the risk of

AF recurrence by 88% (95% CI 15% to 98%; participants = 44; studies = 1; low quality of evidence), with an NNTB of 3.1. No deaths occurred in the studies. No adverse effects of vitamin C were observed in the studies.

In subgroup analyses we found that oral and intravenous vitamin C had different effects on POAF and hospital stay, and that the effect of vitamin C on POAF diverged in studies carried out in the USA and in Iran.

Authors' conclusions

Vitamin C is an essential nutrient that is safe and inexpensive. Given the benefit against the occurrence of AF in the high risk patients and the decrease in hospital stay, 2 g/day vitamin C may be administered for a short period to patients with high risk of AF. Further research is needed to find out the optimal dosage protocol and to identify patient groups that benefit the most.

PLAIN LANGUAGE SUMMARY

Vitamin C may be beneficial for some patients with high risk of atrial fibrillation

Review question

We reviewed the evidence about the effect of vitamin C on atrial fibrillation in people with high risk of atrial fibrillation. We found 14 studies.

Background

We wanted to discover whether using vitamin C was better or worse than placebo or no treatment.

Study characteristics

The evidence is current to Sept 2015. We identified 13 studies with patients who were undergoing cardiac surgery and one study with patients who had been successfully given cardioversion. One of the cardiac surgery studies did not provide numerical data. The total number of participants in the 12 trials included in our meta-analyses was 1641, with about 70% of participants male. The mean age of the participants in the 12 studies ranged from 56 to 73 yr. Essentially all studies on cardiac surgery patients administered 2 g of vitamin C within about 12 hr before the operation and for 5 days after the operation. The cardioversion study administered 2 g vitamin C before the cardioversion and thereafter 1 g/d for seven days. According to the data available to us, none of the trials was funded by pharmaceutical industry.

Key results

Of the 12 studies with cardiac surgery patients, we calculated that vitamin C decreased the risk of AF by 34%. A small study on cardioversion was carried out in Greece and it found about 87% reduction in the recurrence of AF after a successful cardioversion. We found no trials examining the treatment effects of vitamin C on patients with persistent or permanent AF. Nine studies on cardiac patients reported the length of hospital stay and it was 11.4% shorter for the vitamin C groups. Eight studies on cardiac patients reported that the length of intensive care unit stay was 8.8% shorter for the vitamin C groups.

Quality of the evidence

The effects of vitamin C on post-operative AF and on the length of hospital stay and intensive care unit stay have moderate quality of evidence. The effect of vitamin C on recurrence of AF after a successful cardioversion has low quality of evidence since it is based on a single study.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Vitamin C compared with placebo or no-treatment for the secondary prevention of AF

Patient or population: people with high risk of AF
Settings: cardiac surgery or cardioversion
Intervention: vitamin C, oral or intravenous
Comparison: placebo or no-treatment

Outcomes	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
POAF after cardiac surgery	**RR 0.66** (0.57 to 0.77)	1597 (12 studies)	⊕⊕⊕ **moderate**	Heterogeneity over the 12 studies is not high (I^2 = 49%), but there is a systematic difference between trials carried out in Iran and the USA (see text). This led us to decrease the GRADE level since if the effect of vitamin C depends on the cultural context, a single estimate may not be universally applicable
AF recurrence after a successful cardioversion	**RR 0.13** (0.02 to 0.85)	44 (1 study)	⊕⊕ **low**	Although this estimate is based on a single study, the finding is consistent with the set of the 12 studies on the above row
Length of hospital stay (effect in %)	**-11.4%** (-15.2% to -7.6%)	1399 (9 studies)	⊕⊕⊕ **moderate**	Heterogeneity over the 9 studies is not high (I^2 = 31%), but there is a systematic difference between studies that used oral and intravenous vitamin C (see text). This led us to decrease the GRADE level since if the effect of vitamin C depends on the route of administration, a single estimate may not be universally applicable
Length of ICU stay (effect in %)	**-8.8%** (-13.7% to -4.0%)	1061 (8 studies)	⊕⊕⊕ **moderate**	The comment on the above row may apply to this outcome.

AF: atrial fibrillation;**CI:** Confidence interval; **ICU:** intensive care unit; **RR:** Risk Ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Lip 2012; Page 2004). The prevalence of AF increases with age from about 0.1% among adults under 55 years to about 10% in people aged over 80 years (Churg 2014; Go 2001; Perk 2012).

AF is characterized by rapid and irregular activation of the atrium at a rate of > 300 pulses of the atrial muscle wall per minute (Lip 2012). In AF the ventricular rate is determined by the interaction between atrial rate and the filtering function of the atrioventricular node; and the ventricular rate may be about 100 to 150 beats per minute (bpm).

AF can cause palpitations, dyspnea, fatigue, light-headedness and syncope (brief loss of consciousness, or 'fainting') (Page 2004). The more severe consequences of AF are thromboemboli and congestive heart failure (HF). AF may lead to stasis of blood in the atria and clot formation, which may further lead to thromboemboli. Owing to this, AF substantially increases the risk of stroke (Kannel 1998; Perk 2012). AF may also lead to overload on the heart and thereby to HF. Thus, AF is both a cause for, and a result of HF (Wang 2003).

There are over 30 causes for AF, which can be divided into cardiovascular and non-cardiovascular causes (Iqbal 2005). Due to the high frequency in community, hypertension is the most common risk factor for AF and explains over 10% of cases (Kannel 1998; Perk 2012). 'Lone AF' is a term used to describe cases who have no identifiable causes, thus 'lone AF' is a diagnosis based on exclusions (Kozlowski 2009). A further approach to classifying AF is by temporal basis to paroxysmal (self terminating), persistent (lasts > 7 days or requires cardioversion) and permanent (Page 2004).

AF can be triggered by various acute stressful conditions. About 30% of patients in cardiac operations get post-operative AF (POAF) (Hogue 2005), whereas only about 3% of patients in non-cardiac operations get POAF (Bhave 2012). Although AF after cardiac surgery is associated with a longer stay in hospital, it is not clear whether the long stay is caused by AF or whether both of them are caused by other factors which differ between those patients who get AF and those who do not get AF (Levy 2004). Myocardial infarction (MI) may also cause AF, and the combination is associated with higher moratlity than MI alone (Jabre 2011). Heavy exercise may also increase the risk of AF (Abdulla 2009; Turagam 2012).

Although AF is associated with increased morbidity and mortality, arrhythmia suppression is not necessarily a good surrogate for clinical events of importance. Clinical events such as thromboembolism, new or worsening HF and death should be preferred as primary outcomes in studies on AF treatment (Wyse 2004).

Description of the intervention

Vitamin C was identified in the search for the substance which, when deficient in the body, leads to scurvy (Carpenter 1986). This history led to the assumption that the sole physiological function of vitamin C is to prevent and treat scurvy. Therefore, it is often assumed that higher doses of vitamin C cannot be beneficial in a person who does not suffer from scurvy. Due to this history, assessing the role of vitamin C on diseases and conditions other than scurvy is not just an empirical question but also a conceptual issue.

The effects of vitamin C are not limited to the connective tissue, but it is a specific electron donor for enzymes in the synthesis of carnitine, norepinephrine and peptide hormones (Levine 1999). There is also evidence that vitamin C plays a role in the vascular endothelium (May 2013).

Vitamin C is an antioxidant and therefore the effects of supple-

mentation might occur or might be most pronounced under conditions when there is increased oxidative stress in the body.

Aging leads to an increase in oxidative stress (Dai 2009; Toroser 2007). Therefore, vitamin C might have a different influence on the elderly compared with middle-aged and young people. In a large-scale cancer prevention trial amongst smokers, vitamin E decreased mortality in the oldest males only if they had high dietary vitamin C intake (Hemilä 2009a; Hemilä 2011). This modification was specific to vitamin C and was not explained by other substances in fruit, vegetables or berries (Hemilä 2009a). In a meta-analysis of 29 trials, vitamin C was found to reduce blood pressure (Juraschek 2012), but the studies were short. In a meta-analysis of seven trials with patients with atherosclerosis and four trials with patients with HF, vitamin C improved endothelial function (Ashor 2014).

Exercise causes oxidative stress (Powers 2011) which is prevented by vitamin C (Ashton 1999; Silvestro 2002). Thus, vitamin C might affect people who endure heavy physical stress. A meta-analysis of five trials with participants who had short-term heavy physical stress found that vitamin C halved the incidence of common cold symptoms (Hemilä 2013a). A meta-analysis of three trials with participants who suffered from exercise-induced bronchoconstriction found that vitamin C halved the FEV_1 decline caused by exercise (Hemilä 2014). The explanation for these benefits seems to be oxidative stress caused by heavy physical activity.

Infections cause oxidative stress because activated leukocytes release reactive oxygen and nitrogen species (Akaike 2001; Galley 1996). Therefore, vitamin C levels are decreased in various infections (Hemilä 2006). In common cold patients, 6 g/day of vitamin C prevented the decline in vitamin C levels in white blood cells (Hume 1973). Over two dozen trials have shown that vitamin C shortens the duration of colds (Hemilä 2013a) and two trials reported therapeutic benefit for pneumonia patients (Hemilä 2013b).

In two studies vitamin C administration improved the mood of acutely hospitalised patients (Wang 2013; Zhang 2011). Such an effect of vitamin C might be caused by the effects of vitamin C on the brain (Rice 2000). Furthermore, the effects of vitamin C on mood may lead to secondary beneficial effects for hospital patients.

The dose-concentration relation is a relevant issue when considering potential treatment effects of vitamin C. When vitamin C dosage is less than 0.1 g/day, there is steep relationship between plasma vitamin C level and the dosage. For example, when vitamin C dose increases from 0.06 to 0.2 g/day, the level of vitamin C in plasma approximately triples (Levine 1999). In healthy people, plasma vitamin C level reaches saturation at doses of about 1 g/day (Levine 1999). However, there is no basis to assume that the dose-concentration relationship is the same for patients undergoing surgery or for critically ill patients. There is evidence that cardiac and non-cardiac surgery and critical illnesses lead to substantial consumption of vitamin C and low levels in plasma (Ballmer 1994; Berger 2015; Borelli 1996; Long 2003; Rodemeister 2014; Rümelin 2005; Schorah 1996). It is possible that under such conditions the dose-concentration relation differs from healthy people.

The dose-concentration relation is different for oral and intravenous administration. When 1.25 g of vitamin C is given intravenously, plasma peak vitamin C level increases to about 6-fold the level by the same dose orally (Levine 1999; Padayatty 2004). Therefore, intravenous vitamin C has been proposed to be more effective than oral vitamin C (Padayatty 2004). Thus, with a same dose, the two methods of administration might lead to different clinical effects.

Average intake of vitamin C in the USA is currently about 0.1 g/day (IOM 2000). Thus, half of the US population has an intake lower than 0.1 g/day, which means that it is in the range in which the dose has a steep relation with the plasma level. Very low vitamin C intakes are not just of historical interest. Cases of scurvy are being reported even nowadays (e.g. Holley 2011; Smith 2011) and a survey in a French geriatric acute care ward estimated that about 10% of patients had clinical symptoms of scurvy (Raynaud-Simon 2010). In the UK, 25% of men and 16% of women from low-income populations had vitamin C deficiency "(< 11μmol/L) (Mosdøl 2008), and in the USA, 7% of healthy middle-class participants of a survey had vitamin C deficiency (Schleicher 2009). Thus, if low intakes of vitamin C might provide less protection against oxidative stress and thereby might increase the risk of AF, this issue could be important in substantial segments of Western countries.

Approximately 10 mg/day of vitamin C prevents scurvy but the safe dose range extends to grams per day (Hathcock 2005; Hemilä 2006; Levine 1999; IOM 2000). In the US nutritional recommendations, the 'tolerable upper intake level' is stated to be 2 g/day for adults. However, the basis for this upper limit is the appearance of diarrhoea (IOM 2000

Padayatty 2004). Two large-scale trials with 8171 female health professionals and 14,641 male physicians found no adverse effects of 0.5 g/day of vitamin C when administered for 8 to 9 years indicating long term safety of such a dosage level (Cook 2007; Sesso 2008).

Finally, vitamin C is inexpensive and costs pennies per gram. Therefore, its effects might be important even if the size of the effect would not be very large, or if the effects would materialize only in restricted groups of people.

How the intervention might work

In a cell culture study, vitamin C promoted the conversion of mouse fibroblasts into beating cardiomyocytes implying that vita-

) which is a trivial adverse effect

min C might have importance in the cardiac rhythm generation at a fundamental level (Talkhabi 2015).

AF is associated with oxidative stress (Korantzopoulos 2007; Violi 2014), and it seems that the cause-effect relation works in both directions.

There is much evidence from animal studies that tachycardia (rapid heart rate) leads to oxidative stress. In the hearts of dogs artificially kept at rapid ventricular pacing at 240 bpm, the production of superoxide (Ide 1999) and hydroxyl radical (Ide 2000) was increased. In addition, in tachycardic dogs the atrial content of nitrotyrosine was increased and vitamin C level was decreased (Carnes 2001). In rabbits, rapid cardiac pacing increased myocardial oxidative stress as evidenced by the increase in the ratio of oxidized to reduced glutathione and increased level of oxidized mitochondrial DNA (Shite 2001). In pig hearts, experimentally initiated AF increased superoxide production (Dudley 2005). Thus, high cardiac rate appears to cause oxidative stress.

Oxidative stress may, in turn, increase the susceptibility of the heart to tachycardia. In the isolated hearts of aged rats and middle-aged rabbits, hydrogen peroxide exposure increased susceptibility to ventricular tachycardia, whereas in young rats and rabbits it did not cause tachycardia (Morita 2009). Oxidative stress is elevated in several conditions which increase AF risk, such as age (Dai 2009), cardiac surgery (De Vecchi 1998), hypertension (Montezano 2012) and exercise (Powers 2011), and could thus play a role in the emergence of AF.

In humans with AF, oxidative stress was indicated by the increase in the ratio of oxidized to reduced glutathione (Neuman 2007), and decrease in myofibrillar creatine kinase (MM-CK) activity which was inactivated by nitration (Mihm 2001). In the atria of human AF patients the expression of five genes related to the generation of oxidants was increased whereas the expression of two genes related to antioxidants was decreased (Kim 2003). A major source of superoxide in the heart is NADPH oxidase (Montezano 2012), the activity of which was increased in the right atrial appendage of AF patients compared with patients who were in sinus rhythm (SR) (Kim 2005). Although these correlations in human studies indicate association between oxidative stress and AF, the direction of cause is undetermined. Nevertheless, in a further study, high atrial NADPH oxidase level predicted postoperative AF (Kim 2008), which implies that oxidative stress preceded AF.

Several ion channels expressed in the atria are sensitive to the redox state and, therefore, oxidative stress and antioxidants might influence the electrophysiology of atria (Van Wagoner 2008).

Superoxide reacts with nitric oxide to produce peroxynitrite, a strong oxidant. Vitamin C reacts with superoxide (Nishikimi 1975) and with radicals produced by peroxynitrite (Kirsch 2000) and it might thereby influence AF. In tachycardic dogs, vitamin C prevented the increase in nitrotyrosine levels (Carnes 2001). Another study with tachycardic dogs found that the antioxidant N-acetylcysteine (NAC) enhanced recovery of contractile function after a rapid pacing period (Gare 2002).

As described in the previous section, surgery and critical illness in general may decrease vitamin C levels, and some of the studies focused specifically on cardiac surgery patients (Ballmer 1994; Rodemeister 2014). In patients undergoing cardiac operations, vitamin C has increased cardiac perfusion after the operation (Basili 2010) and decreased the level of markers of myocardial injury, such as CK-MB (creatine kinase MB isoenzyme) which often increases with myocardial damage (Albiez 2003; Oktar 2001; Wang 2014).

The first study reporting benefit of vitamin C against POAF was by Carnes 2001. In that trial, which used historical controls, the incidence of POAF was significantly lower in coronary artery bypass graft (CABG) patients administered vitamin C.

A few meta-analyses have concluded that antioxidants in general are effective against POAF (Ali-Hassan-Sayegh 2014; Harling 2011; Violi 2014).

It is possible that vitamin C has different effects on different forms of AF. For example, it seems probable that the effect of vitamin C might be greater on paroxysmal AF than on permanent AF, the latter of which causes structural changes in the heart. It seems also probable that vitamin C has different effects depending on the etiology of AF. In addition, the effects of vitamin C might be most pronounced in patients who have low vitamin C levels.

Why it is important to do this review

AF is the most common of the serious cardiac rhythm disturbances and vitamin C is a safe and inexpensive essential nutrient. The possibility that vitamin C might have preventive or therapeutic effects against AF, even in restricted population groups, is worth examination.

Three previous meta-analyses focused on POAF after cardiac surgery (Ali-Hassan-Sayegh 2014; Harling 2011; Violi 2014). The oldest of them included two randomised trials on vitamin C and POAF. The two later included 3 and 4 randomised trials on vitamin C and POAF, but both of them also included the Carnes 2001 study although it was not randomised. In our review, we identified 13 trials on vitamin C and POAF, thus our review includes 9 to 11 more RCTs than the three previous systematic reviews. In addition, both of the above meta-analyses were restricted to studies on cardiac surgery, whereas we did not set such a restriction. We also identified one study on the effects of vitamin C on the recurrence of AF after a successful cardioversion. Furthermore, a considerable benefit of Cochrane reviews is that they can be kept up to date when new RCTs are published.

No previous Cochrane review has examined the topic of this protocol. Another Cochrane review covers the potential primary preventive effects of vitamin C against cardiovascular diseases including AF (Flowers 2015). In our review we restrict to treatment and secondary prevention, which means population groups with particularly high risk of AF such as after cardiac operations, but our review is not restricted to post-operation AF (POAF). Another

Cohcrane review covers treatment for preventing POAF, but that review does not include vitamin C (Arsenault 2013).
Links to the publications cited in this Background section can be found at http://www.mv.helsinki.fi/home/hemila/CAF.

OBJECTIVES

To assess the efficacy of vitamin C for the secondary prevention of AF and for treating AF.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials on vitamin C which measured AF as an outcome.
For secondary prevention trials, the use of placebo in the control group was not required as it seems unlikely that being aware of taking or not taking vitamin C would influence the occurrence of AF. A recent meta-analysis of trials comparing a placebo group with a no treatment group found evidence that the placebo effect on binary outcomes is small at best (Hrobjartsson 2010). Thus, there is no empirical evidence indicating that the placebo effect might substantially influence the type of outcome as the occurrence of AF.
In our analyses of the length of hospital stay, ICU stay, and mechanical ventilation in the POAF studies, we also did not require placebo. Cardiac surgery patients have a number of drugs and it is highly unlikely that a participant at the ICU or during mechanical ventilation would notice the presence or absence of vitamin C, or that such a notice could influence the duration of ICU stay or mechanical ventilation.
We included trials reported as full-text or abstract, and we included trials that were unpublished.
We studied the influence of methodologically less satisfactory trials by sensitivity analysis.

Types of participants

Secondary prevention

We included trials with people of any age who did not have AF at the baseline, but who had had AF or who have a particularly high risk of AF. We included studies with all types of AF.

Treatment

We included trials with people of any age who have persistent or permanent AF. We included studies with all types of AF.

Types of interventions

The intervention we considered was oral or intravenous administration of vitamin C (ascorbic acid or its salts). We did not set a lower limit to the dose of vitamin C or to the duration of vitamin C supplementation.
The primary focus in this review was on the comparison of vitamin C against a control group with or without placebo, so that all co-interventions are equal in the trial arms. As a secondary focus, we will also include trials comparing vitamin C against standard AF drugs, but we did not identify any.

Types of outcome measures

Primary outcomes

1. Secondary prevention trials: incidence of AF.
2. Treatment trials: incidence of embolic events.
3. Treatment trials: incidence of new HF and worsening of existing HF.
4. All cause mortality.
5. Adverse effects.

Secondary outcomes

1. Secondary prevention trials with POAF patients: length of hospital stay
2. Secondary prevention trials with POAF patients: length of ICU stay
3. Secondary prevention trials with POAF patients: length of mechanical ventilation
4. Treatment trials: return to SR.

If there are data on the effect of vitamin C on quality of life and economic costs, they will be described.
Adverse effects reported in the trials were collected, but we considered that it is unlikely that the trials on AF are informative on safety, given the findings in previous large-scale trials with follow-ups of several years duration (Cook 2007; Sesso 2008) and in short studies with particularly high vitamin C doses (e.g. Padayatty 2004) and other extensive literature on vitamin C safety (Hathcock 2005; Hemilä 2006; Levine 1999; IOM 2000).

Search methods for identification of studies

Electronic searches

We identified trials through systematic searches of the following bibliographic databases on 23 March 2015:

- Cochrane Central Register of Controlled Trials (CENTRAL, Issue 2, 2015) in the Cochrane Library;
- MEDLINE (Ovid, 1946 to March week 3 2015);
- EMBASE (Ovid, 1947 to 2015 March 20).

The search strategies are detailed in Appendix 1. We did not use search filters, but we hand picked trials fulfilling our inclusion criteria.

We also conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) Search Portal (http://apps.who.int/trialsearch/). We used search phrase ["vitamin C" AND fibrillation] on 23 Sept 2015.

We searched all databases from their inception to the present, and we imposed no restriction on the language of publication.

We used the Web of Science 'cited reference search' to identify papers that have cited the included trials as a way to further check that no relevant studies had been missed, e.g. because of miscoding of publications.

Searching other resources

We checked reference lists of all included trials and relevant review articles for additional references. We contacted authors of published studies to ask if they know of ongoing or unpublished trials.

Data collection and analysis

Selection of studies

Two authors (HH, TS) independently screened titles and abstracts for inclusion of the potential trials identified in the literature search, and coded them as 'retrieve' (eligible or potentially eligible) or 'do not retrieve'. If there were disagreements between the two authors at this stage, we retrieved the full paper. For potentially relevant publications, we retrieved the full-text trial reports and abstracts, and two authors (HH, TS) independently screened the reports and identified trials for inclusion, and recorded reasons for exclusion of the ineligible studies. We planned that if we find potentially relevant unpublished results, the two authors will independently consider their inclusion. We resolved any disagreements through discussion. We identified duplicate reports and collated multiple reports of the same trial so that the unit of interest was the trial. We recorded the selection process in sufficient detail to complete a flow diagram and 'Characteristics of excluded studies' table.

Data extraction and management

We used a data collection form for trial characteristics and outcome data. One author (HH) extracted study characteristics from included trials and another author (TS) confirmed the extraction. We extracted the following study characteristics.

1. Methods: study design, total duration of the trial, details of any 'run in' period, trial setting, withdrawals, and date of trial.
2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes of the trial, and time points reported.
5. Potential conflicts of interest: funding for trial and other potential conflicts of interest of trial authors.
6. Additional notes.

One author (HH) extracted outcome data from included trials and another author (TS) confirmed the extraction. If an included trial did not report data in such a way that it could be included in statistical analyses, we narratively described the results in the Results section. We resolved disagreements by discussion. One author (HH) transferred data into Review Manager 5 (RevMan 2012). The second author (TS) checked the entered results against both the original trial reports and our data collection forms. We contacted all authors to ask for more details, see Note sections in Characteristics of included studies.

Assessment of risk of bias in included studies

Two authors (HH, TS) independently assessed the risk of bias for each trial using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion. We assessed the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We graded each potential source of bias as high, low or unclear and provided a quote from the trial report together with a justification for our judgment in the 'Risk of bias' table. We summarized the risk of bias judgements across different trials for each of the domains listed. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.

When we considered intervention effects, we took into account the risk of bias for the trials which contribute to that outcome.

Measures of treatment effect

We analysed dichotomous data on the incidence of AF as risk ratios (RR) with the 95% confidence intervals (95% CI) and continuous data as percentage effects with the 95% CI. For the length of hospital stay, we also calculated the effect on the days the patient stayed at the hospital with the 95% CI. We presented the results in forest plots with a consistent direction so that left from the control group level means benefit of intervention. Transformation to percentage scale is shown in a file available at http://www.mv.helsinki.fi/home/hemila/CAF.

In the Korantzopoulos 2005 study, one cell in the 2 × 2 table had only one case. In such a case the approximate calculation methods of RevMan 2012 (sect 16.9.5) lead to misleading 95% CIs. Therefore, we used the "riskratio.small" program of the R-Project 2015 to calculate the 95% CI for the RR and the Mid-P-value for the comparison. To get the 95% CI for the Number needed to Treat to Benefit (NNTB), the 95% CI for the difference in the proportions of participants who had a recurrence of AF in the Korantzopoulos 2005 was calculated by using the Agresti-Caffo method (Fagerland 2015).

If an included trial did not report data in such a way that it could be presented in a forest plot, the results were narratively described in the Results section.

We planned that if multiple trial arms are reported in a single trial, we will include only the relevant arms. If several arms are relevant, we planned to divide the control group between the intervention arms evenly so that the control participants are not double counted.

We analysed the participants in the groups in which they were allocated. We did not impute outcome values for participants lost to follow-up.

Many studies used Mann-Whitney test in the calculation of the P-values. For skewed data such as the length of hospital stay, Mann-Whitney P-value is preferable to t-test P-values. In some included trials, the Mann-Whitney P-values calculated by the original authors were incompatible with the reported SD values. In addition to skewness, some of the SD values were reported with only one decimal digit and such a rounding is also a possible cause for discrepancy between the reported SD and P-values. Therefore, when appropriate, we adjusted the SD values to reach P-values consistent with the authors' Mann-Whitney P-values. In the Bjordahl 2012 study we adjusted SD for the ventilation time, in the Papoulidis 2011 study we adjusted SD for both hospital stay and ICU stay, and in the Sadeghpour 2015 study we adjusted the SD for the hospital stay, see the Note sections of Characteristics of included studies for details.

We used two-tailed P values in this review.

To simplify our text, when the parenthesis after the point estimate shows the 95% CI limits, we do not always write the term "95% CI" in the parenthesis, when the meaning of the parenthesis is evident.

Dealing with missing data

We contacted investigators to verify key study characteristics and obtain missing outcome data when necessary.

Assessment of heterogeneity

We used the Chi^2 test and the I^2 statistic to assess statistical heterogeneity among the trials in each meta-analysis (Higgins 2003). A value of I^2 greater than about 70% indicates a high level of heterogeneity. If we identified substantial statistical heterogeneity we reported it and explored possible causes by subgroup analyses.

Assessment of reporting biases

We constructed and reported funnel plot for the meta-analysis on the occurrence of AF, although they have been criticized as a tool for assessing whether there is publication bias or not (Ioannidis 2007; Lau 2006; Sterne 2011; Terrin 2005). We follow the instructions of the *Cochrane Handbook for Systematic Reviews of Interventions*: "Results from tests for funnel plot asymmetry should be interpreted cautiously. When there is evidence of small-study effects, publication bias should be considered as only one of a number of possible explanations. In these circumstances, review authors should attempt to understand the source of the small-study effects, and consider their implications in sensitivity analyses." (Higgins 2011).

We also narratively considered the possibility of publication bias in the Discussion section.

Data synthesis

When a group of trials was clinically sufficiently uniform in settings and outcome definitions, and there was no substantial statistical heterogeneity between the results, we pooled the data using the fixed-effect model. If the trials were substantially heterogeneous, either statistically or clinically, we considered whether the studies could not be presented as homogeneous subgroups.

Subgroup analysis and investigation of heterogeneity

We presented clinically different conditions of AF separately as subgroups, such as AF related to cardiac surgery and recurrent AF after a successful cardioversion. We planned that, if there are suitable data available, we were interested in the potential role of age, sex, vitamin C status (important, but rarely reported), and dosage of vitamin C as subgroup variables.

There were not sufficient variation in the vitamin C dose levels so that a subgroup analysis by dosage was meaningful. However, several studies used oral and others used intravenous vitamin C administration and the latter leads to substantially higher plasma levels of vitamin C (Levine 1999, Padayatty 2004). Therefore we carried out subgroup analysis by the method of vitamin C administration. We observed substantial difference between studies

in Iran and in the USA in the effect of vitamin C on POAF occurrence. Therefore we carried out a post hoc subgroup analyses of US vs. non-US studies and Iran vs. non-Iran studies. In our presentations of subgroup differencess, we tested subgroup differences in Review Manager (RevMan 2012).

Sensitivity analysis

We carried out sensitivity analyses by only including trials with a low risk of bias in all of the following items: random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessment, or lack of an explicit placebo, and incomplete outcome data. In sensitivity analyses we excluded Dehghani 2014; Eslami 2007; Healy 2010; Korantzopoulos 2005; Rebrova 2012; Sadeghpour 2015.

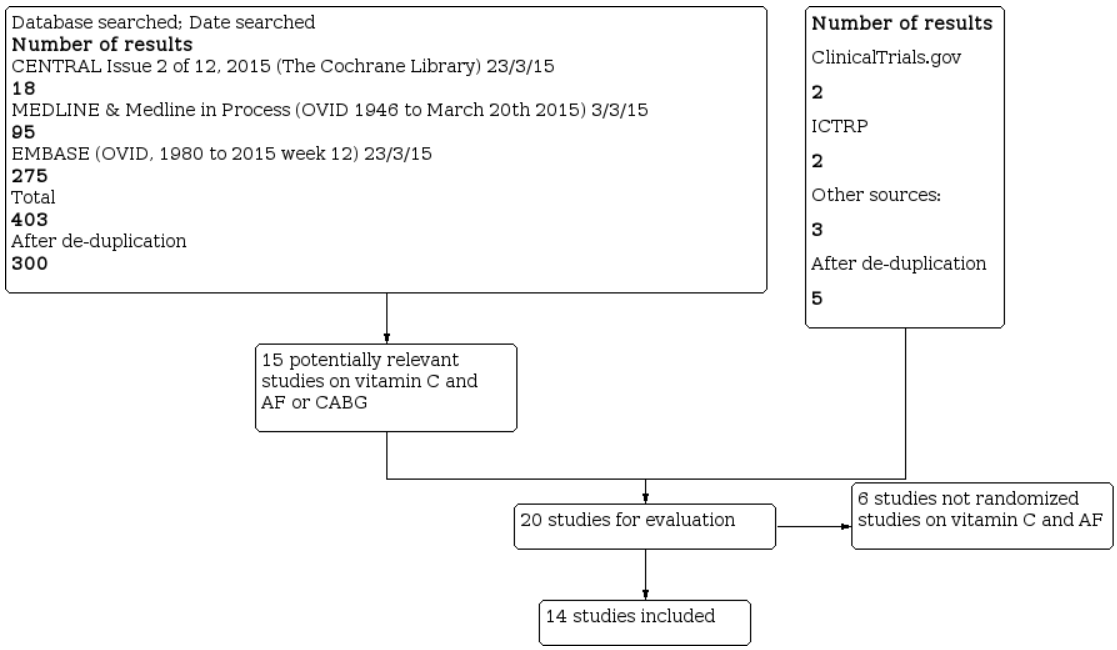
RESULTS

Description of studies

Results of the search

The MEDLINE, EMBASE and CENTRAL searches identified 300 publications after duplicates were removed. By screening of the titles and abstracts, and reading the potentially relevant reports, we identified 15 potentially relevant publications. The ClinicalTrials.gov search identified 2 records of unpublished studies and the ICTRP search identified the same 2 records. In addition, from other sources we identified 3 further potentially relevant studies (Albiez 2003; Rebrova 2012; van Wagoner 2003). These searches identified 14 studies consistent with our inclusion criteria. See Figure 1 for a flow diagram of the searches.

Figure 1. Flow diagram of the searches.



Links to the reports of trials included in and excluded from our review can be found at http://www.mv.helsinki.fi/home/hemila/CAF.

Included studies

Thirteen studies examined the effect of vitamin C on post-operative AF (POAF) after cardiac surgery, either with CABG patients (Bjordahl 2012; Dehghani 2014; Eslami 2007; Papoulidis 2011; Polymeropoulos 2015; Rebrova 2012; Samadikhah 2014; Sarzaeem 2014; van Wagoner 2003) or with CABG and valvu-

lar surgery patients (Healy 2010; Colby 2011; Donovan 2012; Sadeghpour 2015). The 14th included trial examined the recurrence of AF after a successful cardioversion (Korantzopoulos 2005).

Five of the studies were carried out in Iran (Dehghani 2014; Eslami 2007; Sadeghpour 2015; Samadikhah 2014; Sarzaeem 2014), three in Greece (Korantzopoulos 2005, Papoulidis 2011, Polymeropoulos 2015), one in Russia (Rebrova 2012) and five in the USA (Bjordahl 2012; Colby 2011; Donovan 2012; Healy 2010; van Wagoner 2003).

Donovan 2012 study (N = 307) was identified from ClinicalTrials.gov, but we do not have quantitative data. Thus trial is not included in our meta-analyses because of lack of data.

The total number of participants in the 13 trials included in our meta-analyses was 1641, including 874 men and 391 women, while Healy 2010 (N = 30) and van Wagoner 2003 (N = 346) did not report the sex distribution. At the study level, the proportion of males varied from 59% to 100%. There were 794 participants in the vitamin C groups and 847 participants in the placebo groups in the studies for which we have data. The mean age of the participants in the 13 studies ranged from 56 to 73 years.

Essentially all studies on POAF administered 2 g of vitamin C within about 12 hours before the operation and for five days after the operation, and followed for the occurrence of AF for the same period. In most studies vitamin C was administered as tablets, whereas in four studies it was administered intravenously (Papoulidis 2011; Polymeropoulos 2015; Sadeghpour 2015; Sarzaeem 2014).

The cardioversion study by Korantzopoulos 2005 administered 2 g vitamin C before the cardioversion and thereafter 1 g/d for seven days. After a successful cardioversion, participants were followed for one week for the recurrence.

See Characteristics of included studies section for further details of the included trials.

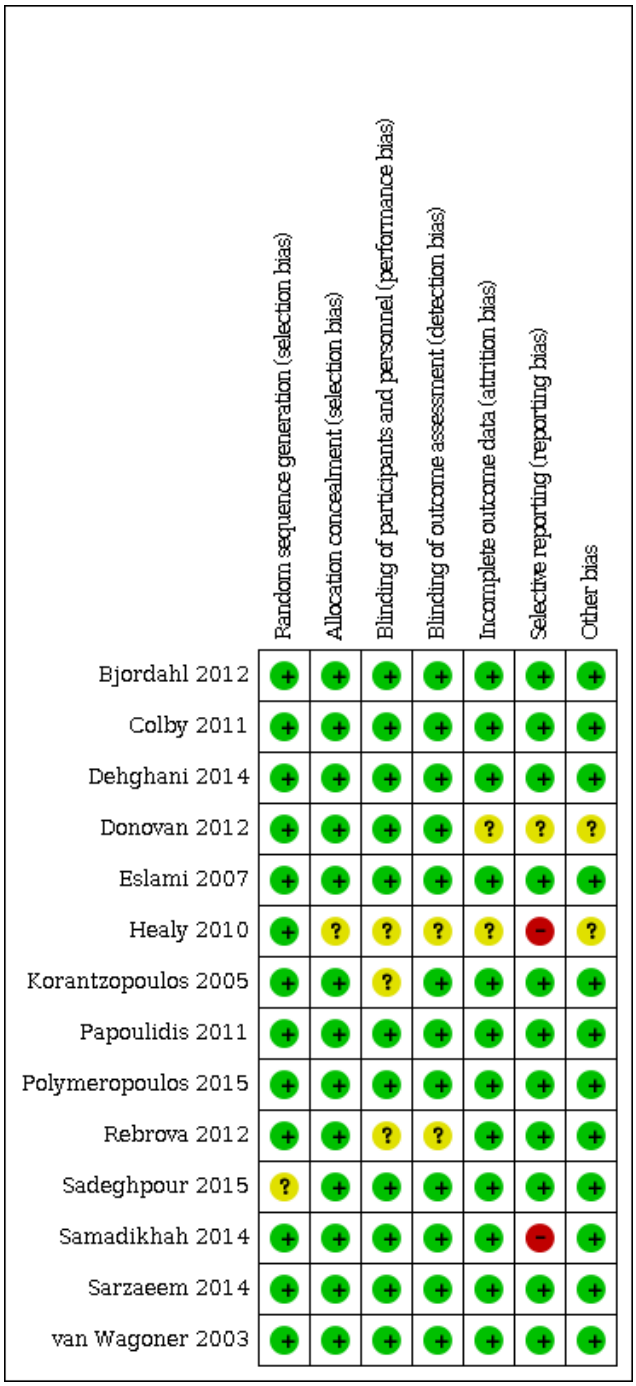
Excluded studies

We excluded seven studies. Five studies administered vitamin C to cardiac patients, but the occurrence of AF was not reported (Albiez 2003; Basili 2010; Dingchao 1994; Oktar 2001; Wang 2014). Dingchao 1994 reported the effect of vitamin C on the length of hospital stay and ICU stay (see Discussion), but it was not a randomised trial. Two studies administered vitamin C to cardiac surgery patients and recorded POAF, but the comparison groups were historical controls and not parallel randomised groups (Carnes 2001; Ibrahim 2010). See Characteristics of excluded studies.

Risk of bias in included studies

See Figure 2 for a summary of the risk of bias assessment.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

By inclusion criteria, all studies were randomized. Sadeghpour 2015 used block randomization, but the difference in the size of the groups is not consistent with block randomization. Therefore, in sensitivity analysis, we excluded the Sadeghpour 2015 study.
Healy 2010 and Rebrova 2012 did not report using allocation concealment, other studies used allocation concealment. Although the other studies did not use the term allocation concealment, double-blinding means that blinding was initiated before allocation and therefore it also indicates that allocation was concealed.

Blinding

Korantzopoulos 2005 described that the patients bought themselves the vitamin C tablets and thus knew to which group they fell to, but the physician who was responsible for cardioversion and follow-up was not aware of the treatment groups.
Dehghani 2014, Eslami 2007, Healy 2010 and Rebrova 2012 did not use a placebo in their cardiac surgery studies. However, cardiac surgery patients are administered a number of drugs and it does not seem likely that a difference in the administration of vitamin C might generate substantial placebo effects during or after surgery, and in an ICU. Furthermore, Hrobjartsson 2010 showed that placebo has minimal or no effects on binary outcomes, such as the occurrence of AF. In other studies participants were blinded for the groups. Rebrova 2012 and Healy 2010 did not report that physicians in charge of treatments and assessment of the outcome were blinded for the groups, but in other studies that was the case. In sensitivity analyses we excluded the Dehghani 2014, Eslami 2007, Healy 2010, Korantzopoulos 2005 and Rebrova 2012 studies.

Incomplete outcome data

None of the studies had substantial or/and unbalanced drop-out rate or rate of withdrawal at the analysis stage.

Selective reporting

Healy 2010 and Samadikhah 2014 write in their text sections that the effect of vitamin C on the length of hospital stay and ICU stay was not significant, but they did not report the data. Otherwise we do not consider that there are concerns with selective reporting.

Other potential sources of bias

The major additional potential source of bias which we considered was funding. None of the studies explicitly reported that the study was funded by pharmaceutical industry, nor did we we find indications in the reports that they were funded by industry. The Dehghani 2014 study was funded by University, the Eslami 2007 study was supported by Tehran University, in the Korantzopoulos 2005 study the patients themselves bought the vitamin C tablets, the Papoulidis 2011 study was self funded, Sadeghpour 2015 paid the study themselves besides getting help from a cardiovascular research center, and the Samadikhah 2014 study was funded by their university.

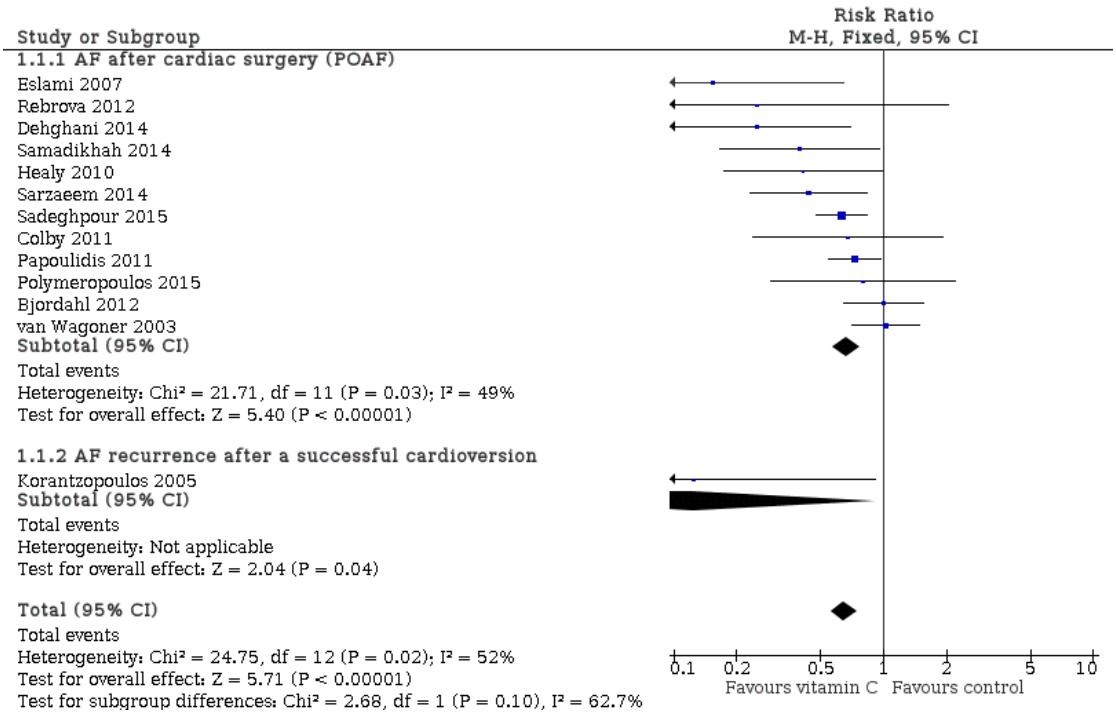
Effects of interventions

See: **Summary of findings for the main comparison**

Prevention of AF in high risk patients

Figure 3 (Analysis 1.1) shows the 13 studies that have reported the effect of vitamin C on the occurrence of AF in high risk patients. Twelve trials examined the occurrence of POAF after cardiac surgery (mainly isolated CABG) and one trial examined the recurrence of AF after a successful cardioversion (Korantzopoulos 2005).

Figure 3. Forest plot of comparison: Effect of vitamin C on AF incidence.



Over the 13 studies, vitamin C decreased the risk of AF by RR 0.65 (95% CI 0.56 to 0.75; participants = 1641; studies = 13; I^2 = 52%). In 11 studies out of 13, the point estimate of effect indicated benefit of vitamin C. Five studies did not find a statistically significant effect of vitamin C. Three of them were particularly small trials with ≤9 POAF cases (Colby 2011; Polymeropoulos 2015; Rebrova 2012), and three were carried out in the USA (Bjordahl 2012; Colby 2011; van Wagoner 2003).

We carried out sensitivity analysis by restricting to studies in which there were no concerns of methodology. In this analysis restricted to seven studies, vitamin C also decreased the occurrence of AF (RR = 0.78; 95% CI 0.64 to 0.93), based on Bjordahl 2012, Colby 2011, Papoulidis 2011, Polymeropoulos 2015, Samadikhah 2014, Sarzaeem 2014, and van Wagoner 2003.

Because of the variation in the clinical context, in further analyses we divided the 13 studies to two subgroups: 1) 12 studies on the occurrence of POAF and 2) one study on the recurrence of AF after a successful cardioversion.

Occurrence of POAF

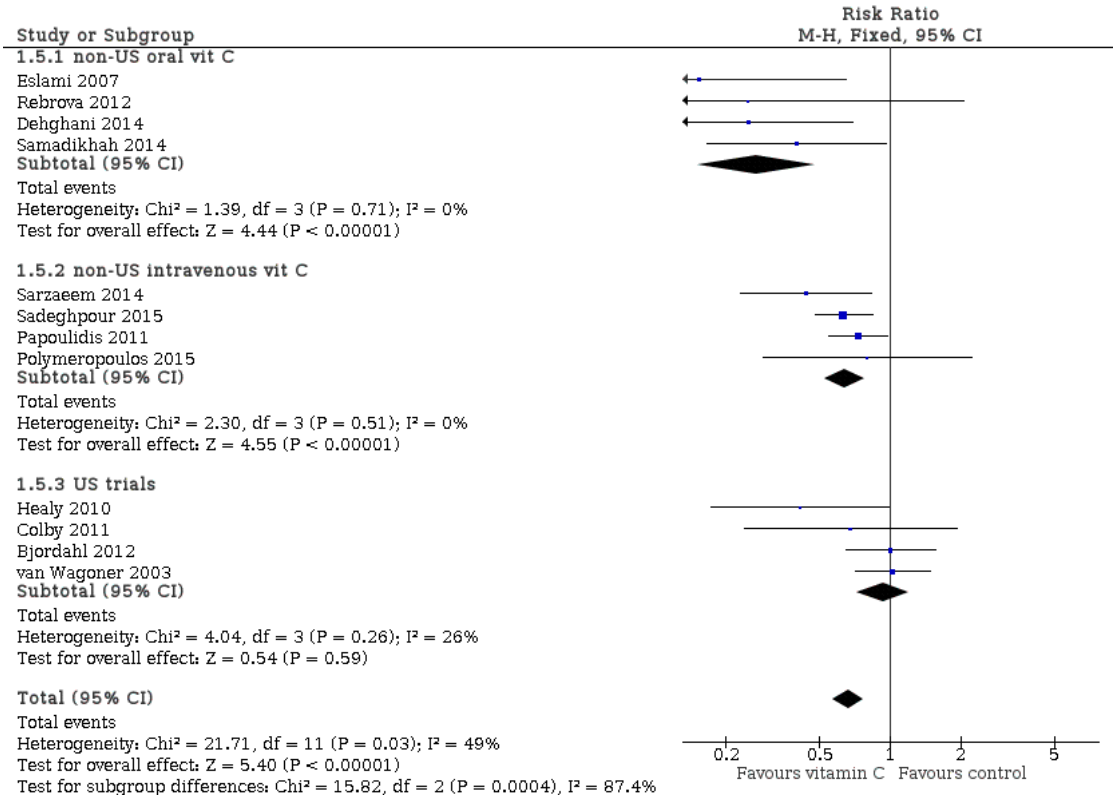
In Subgroup 1 of Analysis 1.1 (Figure 3), in the studies with patients undergoing cardiac surgery, vitamin C decreased the risk of post-operative AF (POAF) by RR 0.66 (0.57 to 0.77; participants = 1597; studies = 12; moderate quality of evidence). There is statistically significant heterogeneity over the 12 studies with I^2 = 49% and Chi^2 test P = 0.03, which suggests that there is no single estimate of effect which is consistent with all the 12 studies. In six studies with POAF that found significant benefit of vitamin C, the Number Needed to Treat to Benefit (NNTB) ranges from 4.2 to 6.6 (Table 1).

In Figure 3, the studies are ordered by the magnitude of the effect by vitamin C. On the bottom of Subgroup 1 are two studies carried out in the USA, neither of which found any benefit of vitamin C (Bjordahl 2012; van Wagoner 2003). Two further US-based studies are small and rather uninformative (Colby 2011; Healy 2010). In contrast, five studies were carried out in Iran and each of them found a significant effect of vitamin C. One study in Russia (Rebrova 2012) and another in Greece (Polymeropoulos 2015) found point estimates favoring vitamin C, but the studies were small and the confidence intervals wide. A larger study in Greece (Papoulidis 2011) found a 27% reduction in POAF occurrence in the vitamin C group. Because of the divergence between the US and Iran studies, we carried out a post hoc subgroup analysis to compare US studies with non-US studies. We included the Russian and Greece studies with the Iran studies.

Analysis 1.2 compares eight studies carried out in countries other than the USA with the four US-based studies. When the pooled effects of the USA trials and the non-US trials are compared, there is strong evidence of heterogeneity between the two sets with I^2 =

90% and Chi^2 test P = 0.001. All the eight non-US studies found a point estimate favoring vitamin C. The pooled effect of the non-US trials indicate that vitamin C decreased the risk of POAF on average by RR 0.55 (0.46 to 0.67; participants = 1012; studies = 8; I^2 = 41%). In contrast, in the four US-based trials, vitamin C had no effect on POAF (RR 0.93, 95% CI 0.72 to 1.21; participants = 585; studies = 4; I^2 = 26%). Within the two groups of countries, there is no substantial evidence of heterogeneity between the trials, and all confidence intervals are consistent with the pooled effect.
In 2009-2012 Donovan 2012 carried out a trial on vitamin C and AF in the USA and it remained unpublished because of negative results. Thus, that study finding is consistent with our calculation for the subgroup of published US-based studies.
As noted above, two studies in Russia and Greece were small and they had a wide confidence interval (Polymeropoulos 2015; Rebrova 2012). Furthermore, the confidence interval for the larger study in Greece (Papoulidis 2011) is consistent with the pooled estimate of the US studies. Therefore we also carried out an analysis of Iran studies against non-Iran studies, which is shown in Analysis 1.3. When the pooled effects of the Iran trials and the non-Iran trials are compared, there is also strong evidence of heterogeneity between the two sets with I^2 = 91% and Chi^2 test P = 0.001. The pooled effect of the five Iran-based trials indicate that vitamin C decreased the risk of POAF on average by RR 0.49 (95% CI 0.39 to 0.62; participants = 780; studies = 5; I^2 = 48%). In contrast, in the non-Iran trials, vitamin C had no effect on POAF (RR 0.84, 95% CI 0.69 to 1.01; participants = 817; studies = 7; I^2 = 9%). Within these two sets of countries, there is also no substantial evidence of heterogeneity between the trials, and all confidence intervals are consistent with the pooled effect.
Both of the two preceding analyses demonstrate the inconsistency of US and Iran studies, whereas the two studies in Greece and the one in Russia are consistent with both US and Iran. A comparison restricted to the four US and the five Iran studies shows heterogeneity of the estimates at level I^2 = 92% and Chi^2 test P = 0.0004.
We planned subgroup analysis by the dose level of vitamin C, but there were no substantial variations in the doses and thus we did not carry out such a subgroup analysis. Nevertheless, most studies used oral vitamin C administration, whereas four studies used intravenous vitamin C administration. These two methods of administration lead to different vitamin C levels in the body and thus we compared them among the non-US studies in Analysis 1.4. Four non-US studies used oral vitamin C administration (Dehghani 2014; Eslami 2007; Rebrova 2012; Samadikhah 2014) and found an effect of vitamin C on POAF by RR 0.27 (0.15 to 0.48; participants = 360; studies = 4; I^2 = 0%). Four non-US studies used intravenous vitamin C administration (Papoulidis 2011; Polymeropoulos 2015; Sadeghpour 2015; Sarzaeem 2014) and found an effect of vitamin C of RR 0.64 (0.53 to 0.78; participants = 652; studies = 4; I^2 = 0%). There is strong evidence of heterogeneity between the two methods of vitamin C administration with I^2 = 87% and Chi^2 test P = 0.006. However, there is no heterogeneity between the trials within the two subgroups by the method of vitamin C administration,
Figure 4 (Analysis 1.5) combines both of the above subgroup analyses: the US studies, non-US oral vitamin C studies and non-US intravenous vitamin C studies. There is strong evidence of heterogeneity in the pooled estimates of the three subgroups with I^2 = 87% and Chi^2 test P = 0.0004.

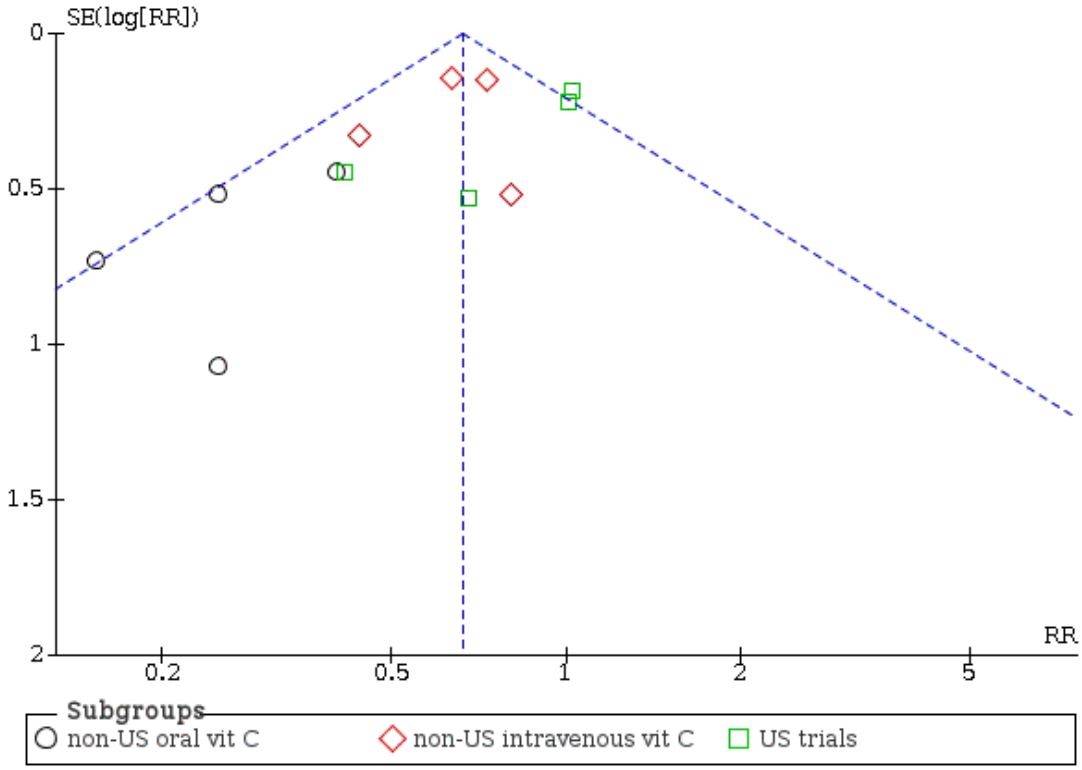
Figure 4. Forest plot of comparison: 1 Occurrence of AF in high risk patients, outcome: 1.5 POAF: Vitamin C effects in subgroups.



Funnel plot

Figure 5 shows a funnel plot of the effect of vitamin C on the occurrence of AF in the 12 cardiac surgery studies. The circles indicate the non-US studies with oral administration, the diamonds indicate non-US studies with intravenous administration, and the squares indicate the US studies. The four non-US studies with oral administration are located on the left side, but there is no basis to assume that the benefit reported in those studies indicates publication bias instead of a greater effect of oral vitamin C administration for non-US cardiac patients.

Figure 5. Funnel plot of comparison: 1 Occurrence of AF in high risk patients, outcome: 1.5 POAF: Vitamin C effects in subgroups.



Recurrence of AF after cardioversion

In Subgroup 2 of Figure 3 there is only one study (Korantzopoulos 2005). The outcome was the recurrence of AF within 1 week after a successful cardioversion. Vitamin C decreased the risk of AF recurrence by 87%.

However, there was only one case of AF in the vitamin C group and thus the 95% CI calculated by RevMan in Figure 3 is misleading. We used the R-Project 2015 package to calculate the small sample confidence interval as RR = 0.12 (0.02 to 0.85; Mid-P = 0.012; participants = 44; studies = 1; low quality of evidence).

In the control group of Korantzopoulos 2005, the incidence of AF recurrence was 36% whereas in the vitamin C group it was 4.5%. The difference between these proportions is 32% (95% CI 7% to 52%). This corresponds to NNTB = 3.1 (95% CI 1.9 to 15).

Length of hospital stay of patients undergoing cardiac surgery

Analysis 2.1 shows the effect of vitamin C on the hospital stay, which we analysed as a secondary outcome. Nine studies reported the duration of hosopital stay, and only the Colby 2011 study did not find point estimate favoring vitamin C, but it had just 24 participants.

On the basis of nine studies, vitamin C shortened the length of hospital stay by 11.4% (7.6% to 15.2%; participants = 1399; studies = 9; I^2 = 31%; moderate quality of evidence). Four of these studies were carried out in Iran, three in the USA, and two in Greece. Of the four studies that found statistically significant benefit of vitamin C, three were carried out in Iran and one in Greece. There is no substantial heterogeneity over the nine studies with I^2 = 31% and Chi^2 test P = 0.2.

In a sensitivity analysis, we restricted to studies with no concerns about methodology. In six studies, vitamin C shortened hospital stay by 13.1% (8.0% to 18.2%), based on Bjordahl 2012, Colby 2011, Papoulidis 2011, Polymeropoulos 2015, Sarzaeem 2014, van Wagoner 2003. This estimate is not smaller than the estimate calculated for all nine studies. Thus, the inclusion of studies with some concerns of methodology do not increase the estimate of effect.

The relative effect in percentages is preferable when different stud-

ies are pooled. The relative effect adjusts for baseline variations in the patient groups. Nevertheless, the absolute effect has more direct practical interpretations. Both of them are informative together.

Analysis 2.2 shows that in the nine studies vitamin C shortened the length of hospital stay by 0.73 days (0.45 days to 1.00 days; participants = 1399; studies = 9). Because of the baseline variations between the trials, we expected greater heterogeneity in the absolute length of hospital stay (in days), and that was observed with I^2 = 57% and Chi^2 test P = 0.02.

Of the 12 studies reporting on POAF occurrence, three did not report the length of hospital stay (Healy 2010; Rebrova 2012; Samadikhah 2014). However, the number of participants in these three studies is only 190, so they are only 12% of all participants in Figure 3. Thus, they do not have statistical power to influence the conclusions on hospital stay even if the effect of vitamin C would be nil in those studies.

Samadikhah 2014 and Healy 2010 write in their text sections that vitamin C did not influence hospital stay, but they did not report the data and the data were not available to us. Nevertheless, the Healy 2010 study was rather small (N = 30 for AF and N = 60 for hospital stay), compared with the majority of studies in Analysis 2.1. Furthermore, Healy 2010 wrote in their abstract that "Median total hospital cost was found to be greater in the control group (p=0.0428)." Thus, it is possible that there was difference in the length of hospital stay in favour of vitamin C, but non-significant because of low power of the study.

Finally, since oral and intravenous vitamin C differed in their effects on the occurrence of POAF, we analysed whether they differ in their effects on hospital stay in Figure 6 (Analysis 2.3). Oral vitamin C decreased hospital stay by 6.3 % (1.2% to 11.4%; participants = 769; studies = 6; I^2 = 0%). Intravenous vitamin C shortened hospital stay by 17.9% (12.1% to 24%; participants = 630; studies = 3; I^2 = 0%). Heterogeneity between the two pooled estimates is high with I^2 = 88% and Chi^2 test P = 0.003. Thus, the two methods of administration have substantially different effects also on this outcome, but the difference in effects is reverse to the effectiveness on the occurrence of POAF in Figure 4.

Figure 6. Forest plot of comparison: 2 Length of hospital stay, outcome: 2.3 Effect of vitamin C in subgroups (in %).

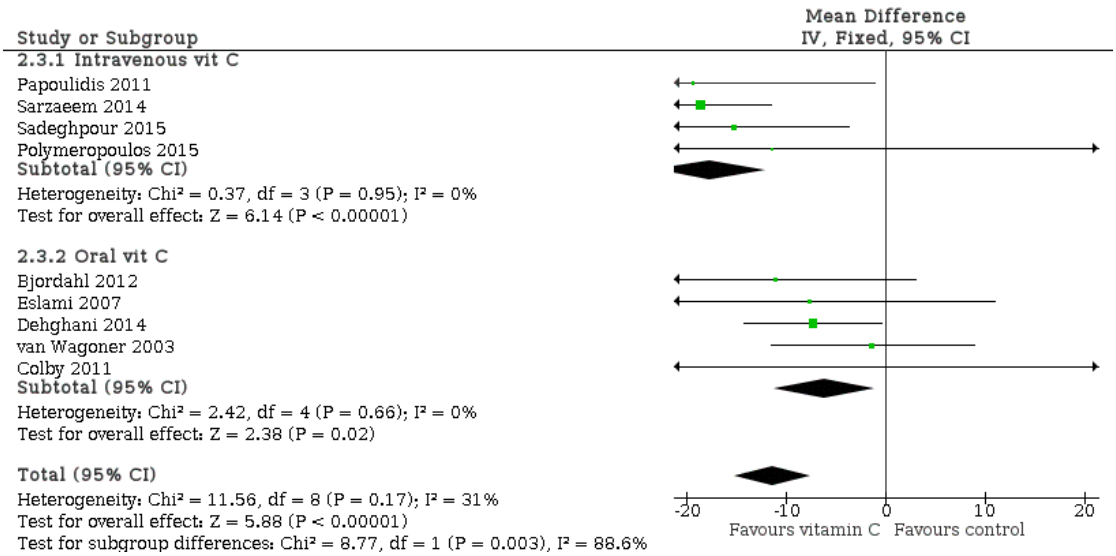
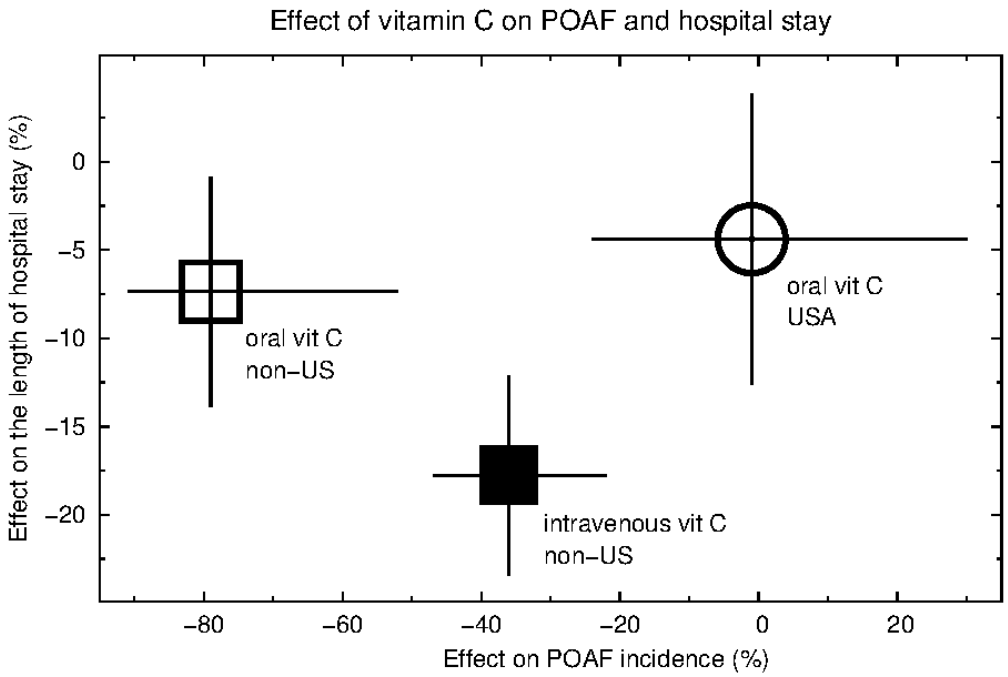


Figure 7 shows the effects of oral and intravenous vitamin C on the POAF occurrence and the length of hospital stay in the studies which have available both outcome values. If POAF is the cause of longer hospital stay, a greater effect by oral vitamin C on POAF occurrence should be associated with a greater effect on the length of hospital stay. However, the reverse is observed for the non-US studies.

Figure 7. Effect of oral and intravenous vitamin C on POAF and on hospital stay. The open square indicates the pooled effect of oral vitamin C in the non-US studies (Dehghani 2014, Eslami 2007) and the filled square indicates the pooled effect of intravenous vitamin C studies in the non-US studies (Papoulidis 2011; Polymeropoulos 2015; Sadeghpour 2015; Sarzaeem 2014). The open circle indicates the pooled effect of oral vitamin C in the US studies (Bjordahl 2012; Colby 2011; van Wagoner 2003). The horizontal and vertical lines indicate the 95% CI ranges for the two effects.



Length of ICU stay of patients undergoing cardiac surgery

Analysis 3.1 shows the effect of vitamin C on the ICU stay, which we analysed as another secondary outcome. In eight studies vitamin C shortened the length of ICU stay by 8.8% (4.0% to 13.7%; participants = 1061; studies = 8; I^2 = 33%; moderate quality of evidence).

Samadikhah 2014 stated that vitamin C did not influence ICU stay, but no data were reported.

Length of mechanical ventilation in patients with cardiac surgery

Analysis 4.1 shows the effect of vitamin C on the ventilation time in four studies which published data on that outcome. According to these studies, vitamin C shortened the length of mechanical ventilation by 15.0% (7.0% to 22.9%; participants = 594; studies = 4; I^2 = 0%).

Mortality

None of the studies reported deaths in the treatment groups.

Adverse effects

None of the included studies reported concerns about possible adverse effects.

Summary of Findings Table

In Summary of findings for the main comparison we describe our evaluation of the evidence of vitamin C effect in secondary

prevention of AF and in affecting the length of hospital and ICU stay.

Treatment of AF

We found no trials examining the treatment effects of vitamin C on patients with persistent or permanent AF.

DISCUSSION

Summary of main results

We found 14 secondary prevention studies with high risk patients and 13 of them were included in our main meta-analysis (Figure 3). These studies test the effect of vitamin C as a secondary prevention against AF in high-risk patients. On average, vitamin C decreased the occurrence of AF by 35%. Vitamin C was effective against post-operative AF (POAF) and against the recurrence of AF after a successful cardioversion.

Twelve studies examined the occurrence of POAF after cardiac surgery and found on average a 36% lower occurrence in vitamin C groups. In six studies in which vitamin C was significantly beneficial, the NNTB ranged from 4.2 to 6.6 (Table 1).

Nine POAF studies reported the length of hospital stay and it was on average 11% (0.73 days) shorter in vitamin C groups. In eight studies, vitamin C shortened the length of ICU stay by 9%. Four studies with cardiac surgery patients found that on average the length of mechanical ventilation was 15% shorter.

One study examined the effect of vitamin C on the recurrence of AF after a successful cardioversion. Vitamin C decreased the recurrence of AF by 88%. The effect of vitamin C corresponds to NNTB = 3.1 (95% CI 1.9 to 15).

We did not find therapeutic vitamin C trials with patients who had persistent or permanent AF.

Overall completeness and applicability of evidence

POAF

Five of the studies in Figure 3 were carried out in Iran and the pooled estimate of effect indicates very strong evidence of preventive effect of vitamin C against POAF (RR = 0.49; 95% CI 0.38 to 0.62). In contrast, four studies in the USA found no benefit of vitamin C against POAF (RR = 0.93; 0.72 to 1.21). We do not consider that methodological differences in the studies is the most reasonable explanation for the inconsistency between these two countries. Instead, it seems plausible that the divergence in the effects of vitamin C is related to cultural and life-style issues.

According to the World Bank, GDP per capita (2010) was $5674 in Iran whereas it was $48,377 in the USA (WB 2015). We do not assume that the GDP per capita directly influences the effects of vitamin C on POAF, but wealth is strongly correlated with cultural and life-style factors including nutrition, and with differences in hospital treatments. Such differences might explain the significant divergence in the effects of vitamin C on POAF between the USA and Iran. The differences in the effects of vitamin C on POAF occurrence in Iran and the US limits the generalization of the findings on AF occurrence.

In two studies carried out in Greece, vitamin C was also effective against AF; against POAF and against the recurrence of AF after cardioversion. In Greece, the GDP per capita (2010) was $26,861 so that it belongs to the less wealthy group of western countries. It does not seem reasonable to assume that the benefits of vitamin C in preventing AF are restricted to Iran and Greece. However, the positive findings in these two countries should not be extrapolated directly to different cultural contexts such as the wealthier countries. Instead, extrapolation from the studies in Iran and Greece may be more reasonable towards less wealthy countries.

Divergence between treatment effects in developing countries and Western countries is not a novel finding. Panagiotou 2013 found several cases in which trials in less developed countries showed significantly more favourable treatment effects than trials in more developed countries. Although such differences may be explained partly by methodological variations in the studies, it is also likely that there are genuine differences between substantially different cultures, in particular in the effects of nutrients such as vitamin C.

In our protocol we planned to carry out subgroup analysis by the level of vitamin C dose, but the doses were so close to each other that such a subgroup analysis would have been uninformative. Nevertheless, there is substantial difference in the pharmacokinetics between oral and intravenous vitamin C (Levine 1999, Padayatty 2004), and intravenous vitamin C may be more reliable for postoperative patients as delayed gastric emptying is a frequent concern. A set of included trials used intravenous and other trials used oral vitamin C administration and therefore we carried out a subgroup analysis contrasting oral with intravenous administration. We restricted to non-US trials with cardiac surgery patients, assuming that the conditions are reasonably similar in studies with such a restriction, so that the variation between oral and intravenous administration is less counfounded by the the great cultural variations between eg USA and Iran. Unexpectedly, we found that oral administration was associated with a much greater benefit against POAF compared with intravenous administration (Figure 4). This finding gives no support to the superiority of intravenous administration to prevent POAF, but the conclusions of this subgroup analysis should be cautious since their are simultaneous other differences between the studies in addition to the route of administration.

Length of hospital stay

Although POAF is associated with a longer stay in the hospital, it is not known whether the long stay is caused by the episode of AF or whether both of them are caused by other factors. Instead of a causal relation, there might be a third factor which could lead to both POAF and a longer hospital stay (Levy 2004). Because of the association between POAF and the longer stay at the hospital, we analysed the effect of vitamin C on hospital stay.

Based on nine studies, we calculated that hospital stay was 11% (0.73 days) shorter in the vitamin C groups. The generalization of this finding involves two questions: 1) is the effect on hospital stay mediated by effects on POAF, or might vitamin C have effects on hospital stay in other severely ill patients unrelated to effects on AF, and 2) are the effects of vitamin C on hospital stay limited to Iran and Greece and comparable countries since in our review the significant findings on hospital stay were observed in those two countries.

As regatrds the first question, a meta-analysis of studies on NAC (N-acetylcysteine) and POAF found that NAC decreased the incidence of POAF with OR = 0.56 (95% CI 0.40 to 0.77) (Ali-Hassan-Sayegh 2014). However, NAC did not decrease the length of hospital stay (SMD: +0.08; 95% CI -0.09 to +0.25). Thus, the decrease in POAF was not associated with a concurrent decrease in the length of hospital stay, and thus the two phenomena may not be causally related although they correlate.

In our analyses, the divergence in the effects of oral and intravenous vitamin C on POAF and on the length of hospital stay in the non-US studies (Figure 7) also conflicts with the notion that POAF per se causes the longer hospital stay. Furthermore, some reports of vitamin C and other antioxidants suggest that they influence the length of hospital stay independent of POAF (see section Agreements and disagreements with other studies or reviews). Therefore, it is possible that the effect of vitamin C on the length of hospital stay in Analysis 2.1 is not, at least fully, explained by its effects on POAF. For example, as mentioned in the background section, there is evidence that vitamin C administration may improve the mood of acutely hospitalised patients (Wang 2013; Zhang 2011) which might also influence the rate of hospital discharge independently of the cardiac status.

As regards the second question, in the USA Bjordahl 2012 found an 11% shorter hospital stay in the vitamin C group. Although difference between the vitamin C and placebo groups was not significant, that estimate of effect is close to the overall estimate of 11.4% in the nine studies included in Analysis 2.1. Furthermore, Bjordahl 2012 found a statistically significant effect of vitamin C on the length of mechanical ventilation. In a few studies in the USA and Japan, vitamin C shortened the length of ICU stay and the duration of mechanical ventilation (see section Agreements and disagreements with other studies or reviews).

Therefore, it seems plausible that the effects of vitamin C on the hospital stay, on the ICU stay and on the length of mechanical ventilation that we found in our analyses of cardiac surgery patients might not be restricted to participants in Iran and Greece and comparable countries, but this effect might have relevance also in more wealthy populations.

In a subgroup analysis we found that intravenous vitamin C was associated with a greater effect on the length of hospital stay compared with oral vitamin C (Figure 6). This is consistent with the suggestion that the effects of intravenous vitamin C may be grater than the effects of oral vitamin C (Padayatty 2004).

The length of hospital stay is determined by numerous factors, many of which might modify the effects of vitamin C. This sets limitations to the generalization of the current findings. Nevertheless, the findings of our review about the length of hispital stay are of practical importance if repeatable in further studies.

Quality of the evidence

As a methodological inclusion criterion, we required that included trials were randomized (Figure 2). In their report, Sadeghpour 2015 write that they used block randomization, but there is a large difference in the size of the groups which is not consistent with block randomization. Rebrova 2012 and Healy 2010 did not report using allocation concealment, but all the other studies used allocation concealment.

Four studies with cardiac surgery patients did not use an explicit placebo (Eslami 2007; Dehghani 2014, Healy 2010, Rebrova 2012). However, in the studies with cardiac surgery patients, other medications serve as a functional placebo to vitamin C. It seems highly unlikely that a cardiac surgery patient could notice whether vitamin C is administered or not along with the other medications, so that the lack of an explicit placebo would substantially bias observations in the Eslami 2007, Dehghani 2014, Healy 2010, and Rebrova 2012 studies.

In the Korantzopoulos 2005 study on the recurrence of AF after cardioversion, patients bought the vitamin C tablets themselves and obviously they were aware to which group they fell to. However, in their Cochrane review, Hrobjartsson 2010 found that placebo has minimal or no effects on binary outcomes, such as the occurrence of AF.

Rebrova 2012 and Healy 2010 did not report that physicians in charge of treatments and assessment of the outcome were blinded for the study groups, but in other studies they were blinded.

Because of the methodologic issues described above, in sensitivity analysis we excluded the Eslami 2007; Dehghani 2014, Healy 2010, Korantzopoulos 2005, Rebrova 2012 and Sadeghpour 2015 studies. The findings on AF occurrence and the length of hospital stay did not change considerably.

The Donovan 2012 and van Wagoner 2003 studies were not published because the results were negative, which are cases of publication bias. Nevertheless, we do not consider that publication bias is a likely explanation for our findings. The evidence of benefit in the non-US studies is very strong and there should be a very large number of unpublished studies in order to explain the positive

findings purely as random variation. Publication bias is a particularly unreasonable explanation for the strong evidence of difference between the oral and intravenous vitamin C administration, and between the US and Iran studies. We do not see any reasonable mechanism how publication bias could lead to the significant differences in those comparisons.

In their text sections, Samadikhah 2014 and Healy 2010 state that vitamin C had no statistically significant effect on hospital stay, but they did not publish the data. That is selective reporting and might bias our estimates. However, in their abstract Healy 2010 wrote that "Median total hospital cost was found to be greater in the control group (p=0.0428)" [based on N = 60]. Thus, it is possible that the study was too small to record a significant effect on the length of hospital stay, but the above sentence does not contradict with benefits on hospital stay.

We do not consider it likely that the significant effects of vitamin C on the occurrence of AF or on the length of hospital stay might be explained by publication bias.

Finally, the 13 studies included in Analysis 1.1 were carried out by 13 different research groups and 7 of those groups found statistically significant findings on the prevention of AF. It does not seem reasonable to assume that all the benefits reported in 7 out of the 13 independent research groups might be caused by hidden systematic biases.

In conclusion, while there are some concerns about internal validity in some of the included studies, our sensitivity analysis indicated that the estimates calculated for all included studies are robust. We do not consider that publication bias is a likely explanation for the reported benefits of vitamin C, or for the differences between the oral and intravenous administration. Nevertheless, we consider that there are limitations in the external validity of the studies, as described in section Overall completeness and applicability of evidence.

Potential biases in the review process

In our protocol, we planned that if there are data on the effect of vitamin C on quality of life and economic costs, they will be described. After seeing the included studies we found that several of them had recorded the length of hospital stay, length of ICU stay, and a few had recorded the length of mechanical ventilation. We had not listed these three outcomes in our protocol. However, they may be considered as operational forms of quality of life and economic costs and in that respect they are not inconsistent with out protocol.

In our procotol, we also planned that if there are suitable data available, we were

interested in the potential role vitamin C status as a subgroup variable. We noted that vitamin C status is important, but rarely reported. None of the included studies reported vitamin C status of the patients. After seeing the included studies we observed that there was substantial divergence in the effects of vitamin C in the US studies and in the Iran studies and we decided to carry out a post hoc subgroup analysis by the countries so that we contrasted US and non-US studies, and Iran and non-Iran studies. One possible explanation for the differences between Iran and USA is dietary vitamin C intake, but there are numerous other differences between those two countries. Although these comparisons were carried out as post hoc analyses after seeing the data, the divergence between the US and Iran studies is so great that the finding is not reasonably explained by the multiple comparison problem.

We re-considered the possibility of placebo effect influencing the length of mechanical ventilation, the length of ICU stay, and the length of hospital stay, and it seemed to us highly unlikely that the absence of explicit placebo might influence such outcomes. Nevertheless, we carried out sensitivity analysis and excluded trials that did not use placebo from our analysis of hospital stay, which we consider the most important of these three outcomes.

Agreements and disagreements with other studies or reviews

Vitamin C is an antioxidant and therefore the effects of other antioxidants are of interest. Given that cardiac operations increase oxidative stress, antioxidants in general might be beneficial against POAF. A few previous meta-analyses have found strong evidence that antioxidants vitamin C, vitamin E, NAC reduce the risk of POAF (Ali-Hassan-Sayegh 2014; Harling 2011; Violi 2014). In this respect our findings about vitamin C are consistent with findings about different antioxidants and their combinations.

Furthermore, 12 studies included in Figure 3 examined cardiac surgery patients. Thus, other studies with surgical patients and other seriously ill patients are relevant in parallel. In China, Dingchao 1994 administered vitamin C to cardiac surgery patients and reported that the stay at hospital was 37% (P= 0.07) shorter and the stay at ICU was 44% (P = 0.04) shorter in the vitamin C group. In Japan, Tanaka 2000 studied the effect of vitamin C on severely burned patients and found that the length of hospital stay was 18% shorter (P = 0.4) and the length on mechanical ventilation was 43% shorter (P = 0.03). In Russia, Mochalkin 1970 reported up to 36% (P < 0.001) shorter hospital stay in pneumonia patients administered vitamin C (see Hemilä 2013b). In critically ill surgical patients, the combination of vitamins C and E (Nathens 2002) shortened the ICU stay by 1.2 days (95% CI 0.8 to 1.5 days; P < 0.001). Finally, in a case-control study, acutely injured patients who were administered vitamins C and E and selenium had a 33% (1 day; P < 0.001) shorter median length of stay in the ICU and a 25% (1 day; P < 0.001) shorter median length of stay in the hospital (Collier 2008). The latter study also found a significantly lower mortality in the antioxidant group corresponding to NNT = 17 to 43 (Hemilä 2009b).

Thus our calculations about the the effects of vitamin C on the length of hospital stay, ICU stay, and mechanical ventilation from the studies on vitamin C and POAF are conceptually consistent

with a few other studies on vitamin C alone or vitamin C with other antioxidants administered to severely ill patients.

Our review was formulated as an examination of effects of vitamin C on the occurrence of AF in people with high risk. Patients undergoing cardiac surgery or cardioversion may suffer from acute oxidative stress and therefore vitamin C may be effective in such special conditions. However, it seems evident that the findings cannot be generalized to ordinary people with a good health. Sesso 2008 studied the primary prevention effects of vitamin C on US physicians and found no effects on cardiac diseases, though the rate of AF was not reported. However, the participants of the study and their living conditions were so different from the studies included in our review, that the Sesso 2008 study should not be considered as being inconsistent with our review.

Protocol for vitamin C dosage

In the first ever study on vitamin C for preventing POAF, Carnes 2001 described their vitamin C protocol as follows: "patients scheduled for primary CABG surgery were given 2 g ascorbic acid (extended release) the night before surgery, followed by 500-mg doses twice daily for the 5 days after surgery". The Carnes 2001 study was not a randomized trial and therefore it was excluded from our meta-analyses. Nevertheless, all subsequent dosage protocols of administering vitamin C to cardiac surgery patients are only minor modifications of the protocol used by Carnes 2001.

Although the first question after the publication of a positive result should be whether the result can be repeated, subsequent studies should also be extended to investigate optimal dosages and the factors influencing the magnitude of the effect instead of just repeating the first protocol.

Vitamin C is water soluble and its concentration in plasma increases within 1-2 hours after oral administration and thereafter the levels are decreased (Levine 1999; Padayatty 2004). On the basis of such pharmacokinetics, it seems unlikely that a longer administration before the cardiac operation might lead to further benefit. In three studies, vitamin C was administered 3 hours before the operation (Papoulidis 2011), "in the operation day" (Samadikhah 2014), or "immediately before surgery" (Sadeghpour 2015) and all of them found significant effect of vitamin C (Figure 4).

Oktar 2001 administered intravenously 4 g of vitamin C to cardiac surgery patients and compared the difference between administration before anesthesia and administration immediately before the cardiopulmonary bypass. The earlier administration led to significantly smaller CK-MB decreases after the operation. Thus, too later vitamin C adminstration may not lead to smaller benefits.

Relevant data about timing and clinical effects of vitamin C are also available from trials in which vitamin C protected against exercise-induced bronchoconstriction. In two studies vitamin C was administered 1-1½ hours before the exercise challenge test indicating that a longer supplementation was not needed before the condition that caused oxidative stress (Hemilä 2014). Therefore it seems probable that a single high dose vitamin C a few hours before a cardiac operation may be sufficient, and a longer administration before the operation may not lead to a greater benefit.

In the dosage protocols of the included POAF trials, vitamin C administration was continued for 5 days after the operation. Assuming that the greatest peak of oxidative stress occurs during and soon after the operation, a shorter administration after the operation might be sufficient and should be investigated.

The 1-2 g/day dose level of vitamin C used in the POAF trials we include in our review is not based on any research data, but simply traces to the Carnes 2001 study. In healthy people, a single 3 gram oral vitamin C leads to a higher plasma peak level compared with a single 1 gram dose. However, 3 gram doses 6 times per day leads to sustained high levels of vitamin C in plasma, of approximately 200 μmol/L (Padayatty 2004). Furthermore, intravenous administration of 50-100 grams of vitamin C can lead to plasma levels of up to 1000-1500 μmol/L (Padayatty 2004). These dose-concentration relations are based on investigation of healthy people. However, as described in the Background section, there is evidence that vitamin C is consumed in surgical operations and in serious illness and therefore the dose-concentration relations may differ in such conditions compared with healthy people. Furthermore, the optimal concentration of vitamin C during cardiac operations is not known, and it should not be assumed that a higher level is unambiguously better.

In addition to the difference in the pharmacokinetics between oral and intravenous vitamin C, intravenous administration of vitamin C may be a more reliable route in postoperative patients as delayed gastric emptying is frequently seen after cardiac surgery.

The divergence we found in the effects of oral and intravenous vitamin C administration indicates that the two routes of vitamin C administration should be further studied by head-to-head comparisons in 3-arm randomized trials instead of just comparing studies that have various other differences simultaneously. Various dose levels should also be compared to find out whether doses higher than 2 g/day might lead to greater benefit.

Possible heterogeneity in vitamin C effects on diverse outcomes

One particularly important finding in our study was the substantial variation in the effects of vitamin C by the location of the study (US vs non-USa) and by the method of administration of vitamin C (oral vs intravenous) (Figure 4 and Figure 7). Substantial heterogeneity in the effects of vitamin C has been found previously and they indicate that heterogeneity should be expected in many effects of the vitamin. One factor that may explain heterogeneity in vitamin C supplementation effects is variation in the level of oxidative stress, and another factor is variation in the level of dietary vitamin C intake.

Cochrane review on vitamin C and the common cold found that vitamin C does not influence the average incidence of colds in the

general community, but in five trials it halved the incidence of colds in people who were under heavy short-term physical stress (Hemilä 2013a). A 4-month trial on 154 British asthmatics showed that 1 g/day of vitamin C did not influence the FEV_1 level (Fogarty 2003), whereas three small trials found that vitamin C halved the FEV_1 decline associated with exercise-induced bronchoconstriction (Hemilä 2014). In both of these two cases, the benefit of vitamin C was associated with heavy physical activity, which is known to increase oxidative stress level (Powers 2011). The effects of vitamin C in physically very active persons seem genuine effects, but they cannot be generalized to sedentary people.

A meta-analysis of four trials with British men calculated that vitamin C significantly decreased common incidence on average by 30% and the explanation for that positive finding appeared to be the particularly low dietary vitamin C intake in the UK when the four studies were carried out in the 1940s to 1970s (Hemilä 1997). There is also evidence of sex differences in the effects of vitamin C on common cold incidence so that the effect seems to be greater in males (Hemilä 1997; Hemilä 2008).

Cochrane review on vitamin C and pneumonia found three trials in which vitamin C significantly decreased the incidence of pneumonia by ≥80% (Hemilä 2013b). While the effect of vitamin C seemed genuine in the three trials, the conditions were extraordinary, such as boys in a boarding school in the UK during WWII and US Marines during their recruit training. It is evident that such findings cannot be extrapolated to the current general Western population. In particular, a large US cohort study found no association between dietary vitamin C intake and the incidence of pneumonia in male US health professionals of 40 to 75 years of age, the selection of which meant a population with a much greater than average interest in factors that affect health and whose working conditions are quite sedentary (Merchant 2004). Furthermore, in that cohort of health professionals, the median vitamin C intake of the lowest quintile was 95 mg/day and the overall median was 218 mg/day, whereas the overall median of the ordinary US population is about 100 mg/day (IOM 2000). Thus, that cohort analysis does not test whether vitamin C might be beneficial for population groups that have a particularly low vitamin C intake, or particularly heavy physical stress.

Padayatty 2014 pointed out that a universal problem with vitamin C trials is the lack of examination of the baseline vitamin C status so that the possible effects could be correlated with the initial vitamin C levels. This is also true for all the studies which we included in this review. None of them measured vitamin C plasma levels or estimated dietary vitamin C intake of the participants. Based on the previous evidence of heterogeneity in vitamin C effects, we planned in our protocol to carry out subgroup analysis by dietary vitamin C intake and sex. However, the reports did not provide appropriate data for either analysis. We cannot assess whether the dramatic difference between the US and Iran studies might be explained, at least in part, by differences between vitamin C intake or other differences in nutrition.

Our subgroup analysis in Figure 4 was not preplanned in our protocol. However, as described above, we expected heterogeneity in the effects of vitamin C on AF, and the factors used for the division of studies to subgroups in Figure 4 are reasonable when considering prior knowledge about vitamin C, and the observed variation in treatment effects between less developed and more developed countries (Panagiotou 2013). That subgroup analysis seems much more informative when we try to understand the effects of vitamin C, compared with the pooling of all POAF studies together as in our Figure 3.

Figure 4 and Figure 7 instruct directions for further research on vitamin C and AF. They indicate that future studies should directly compare oral and intravenous administration. In addition, it does not seem reasonable to carry out further studies in wealthier countries without measuring vitamin C status of patients and specifically restricting to those who have a particularly low vitamin C status.

The notion that various factors may modify the effects of vitamin C on AF and other conditions is fundamentally important in restricting broad generalisations from individual trials, irrespective of whether the finding is positive or negative, and whether or not the trial is large and carefully conducted.

Safety of vitamin C

In general, vitamin C is considered safe in doses up to several grams per day. Although there have been speculations of potential harms of large doses they have been shown to be unfounded (Hathcock 2005; Levine 1999; IOM 2000).

In the US, the average vitamin C intake is about 0.1 g/d (IOM 2000

IOM 2000), and the basis for that level is diarrhoea, which is a trivial and short-lasting adverse effect. Some physicians have administered their patients tens of grams of vitamin C per day without adverse effects (Cathcart 1981; Padayatty 2010

). Although such a review included trials to provide evidence about dose-response

out in Iran and Greece, oral 1-2 g vitamin C may be administered for a short period to patients with high risk of AF in less affluent countries. The lack of benefit in the studies carried out in the USA suggests that vitamin C may not prevent AF in wealthy countries.

The consistent effect of vitamin C on the length of hospital stay and ICU stay of cardiac surgery patients indicates that vitamin C may be administered for cardiac surgery patients in the dose of 1-2 g/day.

Although our findings, and the safety and low cost of vitamin C allows such implications, more specific recommendations require evidence from larger trials.

Implications for research

Although the evidence for benefit of vitamin C in preventing AF is very strong from the studies carried out in Iran and in Greece, the studies are quite small and many of them were poorly reported. In addition, all studies have used essentially the same protocol. Studies should be carried out to find out the optimal protocol for vitamin C administration and to find out which patient groups get most benefit, eg by examining vitamin C status before a cardiac operation or a cardioversion.

In wealthier countries, the effect of vitamin C against AF in high risk patients should be tested on patients who have documented low level of vitamin C, but not on unselected patients.

The effect of vitamin C on the length of hospital stay and ICU stay should be examined along with its effects on AF. However, the effect of vitamin C on the length of hospital stay and ICU stay should be studied also in other severely ill patients.

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REFERENCES

References to studies included in this review

Bjordahl 2012 *{published data only}*
Bjordahl PM, Helmer SD, Gosnell DJ, Wemmer GE, O'Hara WW, Milfeld DJ. Perioperative supplementation with ascorbic acid does not prevent atrial fibrillation in coronary artery bypass graft patients [discussion on p. 867]. *American Journal of Surgery* 2012;**204**(6):862–7. [DOI: 10.1016/j.amjsurg.2012.03.012; PUBMED: 23022248]

Colby 2011 *{published data only}*
Colby JA, Chen WT, Baker WL, Coleman CI, Reinhart K, Kluger J, et al. Effect of ascorbic acid on inflammatory markers after cardiothoracic surgery. *American Journal of Health-System Pharmacy* 2011;**68**(17):1632–1639. [DOI: 10.2146/ajhp100703; PUBMED: 21856809]

Dehghani 2014 *{published and unpublished data}*
Dehghani MR, Madjidi N, Rahmani A, Asgari B, Rezaei Y. Effect of oral vitamin C on atrial fibrillation development after isolated coronary artery bypass grafting surgery: A prospective randomized clinical trial. *Cardiology Journal* 2014;**21**(5):492–499. [DOI: 10.5603/CJ.a2013.0154; PUBMED: 24293167]

Donovan 2012 *{unpublished data only}*
Donovan PC, Kramer RS. Prophylaxis to Reduce Postoperative Atrial Fibrillation in Cardiac Surgery. ClinicalTrials.gov 2012. [: https://clinicaltrials.gov/ct2/show/study/NCT00953212]

Eslami 2007 *{published and unpublished data}*
Eslami M, Badkoubeh RS, Mousavi M, Radmehr H, Salehi M, Tavakoli N, et al. Oral ascorbic acid in combination with beta-blockers is more effective than beta-blockers alone in the prevention of atrial fibrillation after coronary artery bypass grafting. *Texas Heart Institute Journal* 2007;**34**(3):268–74. [: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1995047; PUBMED: 17948074]

Healy 2010 *{published data only}*
Healy RM, Day D, Van Gorder C. Ascorbic acid utilization for atrial-fibrillation prophylaxis post coronary-artery-bypass graft and valve replacement surgeries: An interim analysis of a prospective, randomized study [Abstract 285]. *Pharmacotherapy: The Journal of Human Pharmacology & Drug Therapy* 2010;**30**(10):445e–446e. [DOI: 10.1592/phco.30.10.1086]

Korantzopoulos 2005 *{published and unpublished data}*
Korantzopoulos P, Kolettis TM, Kountouris E, Dimitroula V, Karanikis P, Pappa E, et al. Oral vitamin C administration reduces early recurrence rates after electrical cardioversion of persistent atrial fibrillation and attenuates associated inflammation. *International Journal of Cardiology* 2005;**102**(2):321–6. [DOI: 10.1016/j.ijcard.2004.12.041; PUBMED: 15982504]

Papoulidis 2011 *{published and unpublished data}*
* Papoulidis P, Ananiadou O, Chalvatzoulis E, Ampatzidou F, Koutsogiannidis C, Karaiskos T, et al. The role of ascorbic acid in the prevention of atrial fibrillation after elective on-pump myocardial revascularization surgery: A single-center experience - a pilot study. *Interactive Cardiovascular and Thoracic Surgery* 2011;**12**(2):121–4. [DOI: 10.1510/icvts.2010.240473; PUBMED: 21098510]
Papoulidis P, Chalvatzoulis E, Ananiadou O,

Koutsogiannidis H, Karfis E, Madesis A, et al. Can ascorbic acid prevent the onset of postoperative atrial fibrillation? [Abstract O-41]. *Journal of Cardiothoracic and Vascular Anesthesia* 2009;**23**:S18. [DOI: 10.1053/j.jvca.2009.04.010]

Polymeropoulos 2015 *{unpublished data only}*
Polymeropoulos E. Vitamin C for Prophylaxis of Post-operative Atrial Fibrillation in On-pump Cardiac Surgery Procedures. ClinicalTrials.gov 2015. [: https://clinicaltrials.gov/ct2/show/NCT01107730]

Rebrova 2012 *{published and unpublished data}*
Rebrova TY, Shipulin VM, Afanasev SA, Vorobeva YB, Kiyko OG. The experience of the application of ascorbinic acid as antioxidant after coronary artery surgery with use of cardiopulmonary bypass [in Russian; English translation is available]. *Kardiologija* 2012;**52**(7):73–6. [: http://www.mv.helsinki.fi/home/hemila/T12.pdf; PUBMED: 22839718]

Sadeghpour 2015 *{published and unpublished data}*
Sadeghpour A, Alizadehasl A, Kyavar M, Sadeghi T, Moludi J, Gholizadeh F, Totonchi Z, Ghadrdoost B. Impact of vitamin C supplementation on post-cardiac surgery ICU and hospital length of stay. *Anesthesiology and Pain Medicine* 2015;**5**(1):e25337. [DOI: 10.5812/aapm.25337; PUBMED: 25789244]

Samadikhah 2014 *{published and unpublished data}*
Samadikhah J, Golzari SEJ, Sabermarouf B, Karimzadeh I, Tizro P, Khanli HM, et al. Efficacy of combination therapy of statin and vitamin C in comparison with statin in the prevention of post-CABG atrial fibrillation. *Advanced Pharmaceutical Bulletin* 2014;**4**(1):97–100. [DOI: 10.5681/apb.2014.015; PUBMED: 24409416]

Sarzaeem 2014 *{published data only}*
Sarzaeem M, Shayan N. Vitamin C in prevention of atrial fibrillation after coronary artery bypass graft: Double blind randomized clinical trial [in Farsi (Persian) with and English abstract; English translation of full paper is available]. *Tehran University Medical Journal* 2014;**71**(12):787–793. [: http://tumj.tums.ac.ir/browse.php?a˙code=A–10–25–5176&slc˙lang=en&sid=1; : http://www.mv.helsinki.fi/home/hemila/T14.pdf]

van Wagoner 2003 *{unpublished data only}*
Van Wagoner DR. Oxidative stress and inflammation in atrial fibrillation: role in pathogenesis and potential as a therapeutic target. *Journal of Cardiovascular Pharmacology* 2008;**52**(4):306–13. [DOI: 10.1097/FJC.0b013e31817f9398; PUBMED: 18791466]
* Van Wagoner DR, Palumbo R, Li J, Carnes CA, Gillinov M, McCarthy PM, Chung MK. Supplemental Vitamin C did not Reduce the Incidence of Atrial Arrhythmia Following CardiacBypass Surgery. Abstract to Heart Rhytm Society in 2003; not published 2003.

References to studies excluded from this review

Albiez 2003 *{published data only}*
* Albiez GA, Preiss DU, Cap, M, Tollenaere PL, Wartenberg-Demand A. High-dose intravenous ascorbic acid reduces platelet loss and ischemic events during coronary bypass surgery - a single-centre, double-blind, randomised study. Perfusion. 2003; Vol. 16, issue 1:4.
Albiez GA, Preiss DU, Jaehnchen E, Cap M, Tollenaere PJ. High Doses of Ascorbic Acid Diminish Platelet Loss and Accelerate Return to Normal Following Cardiopulmonary Bypass [Abstract]. American Society for Anesthesiologists 2000 Annual Meeting Abstracts. 2000:A–177.

Basili 2010 *{published data only}*
Basili S, Tanzilli G, Mangieri E, Raparelli V, Di Santo S, Pignatelli P, et al. Intravenous ascorbic acid infusion improves myocardial perfusion grade during elective percutaneous coronary intervention: relationship with oxidative stress markers. *Journal of the American College of Cardiology cardiovascular interventions* 2010;**3**(2):221–9. [DOI: 10.1016/j.jcin.2009.10.025; PUBMED: 20170881]

Carnes 2001 *{published data only}*
Carnes CA, Chung MK, Nakayama T, Nakayama H, Baliga RS, Piao S, et al. Ascorbate attenuates atrial pacing-induced peroxynitrite formation and electrical remodeling and decreases the incidence of postoperative atrial fibrillation. *Circulatory Research* 2001;**89**(6):E32–8. [DOI: 10.1161/%E2%80%8Bhh1801.097644; PUBMED: 11557745]

Dingchao 1994 *{published data only}*
Dingchao H, Zhiduan Q, Liye H, Xiaodong F. The protective effects of high-dose ascorbic acid on myocardium against reperfusion injury during and after cardiopulmonary bypass. *Thoracic and cardiovascular surgeon* 1994;**42**(5):276–8. [DOI: 10.1055/s-2007-1016504; PUBMED: 7863489]

Ibrahim 2010 *{unpublished data only}*
Ibrahim TM, Hill PC, Bafi AS, Kanda LT, Ellis JL, Lowery RC, et al. The effect of vitamin C on the incidence of atrial fibrillation after major cardiac surgery [Abstract]. *Chest* 2010;**138**(4):503A. [DOI: 10.1378/chest.10443]

Oktar 2001 *{published data only}*
Oktar GL, Sinci V, Kalaycioglu S, Soncul H, Gökgöz L, Halit V, Ersöz A. Biochemical and hemodynamic effects of ascorbic acid and alpha-tocopherol in coronary artery surgery. *Scandinavian Journal of Clinical and Laboratory Investigation.* 2001;**61**(8):621–9. [DOI: 10.1080/003655101753267982; PUBMED: 11768322]

Wang 2014 *{published data only}*
Wang ZJ, Hu WK, Liu YY, Shi DM, Cheng WJ, Guo YH, et al. The effect of intravenous vitamin C infusion on periprocedural myocardial injury for patients undergoing elective percutaneous coronary intervention. *Canadian Journal of Cardiology* 2014;**30**(1):96–101. [DOI: 10.1016/j.cjca.2013.08.018; PUBMED: 24365194]

Additional references

Abdulla 2009
Abdulla J, Nielsen JR. Is the risk of atrial fibrillation higher in athletes than in the general population? A systematic review and meta-analysis. *Europace* 2009;**11**(9):1156–9. [DOI: 10.1093/europace/eup197; PUBMED: 19633305]

Akaike 2001
Akaike T. Role of free radicals in viral pathogenesis and mutation. *Reviews in Medical Virology* 2001;**11**(2):87–101. [DOI: 10.1002/rmv.303; PUBMED: 11262528]

Ali-Hassan-Sayegh 2014
Ali-Hassan-Sayegh S, Mirhosseini SJ, Rezaeisadrabadi M, Dehghan HR, Sedaghat-Hamedani F, Kayvanpour E, et al. Antioxidant supplementations for prevention of atrial fibrillation after cardiac surgery: an updated comprehensive systematic review and meta-analysis of 23 randomized controlled trials. *Interactive cardiovascular and thoracic surgery* 2014;**18**(5):646–54. [DOI: 10.1093/icvts/ivu020; PUBMED: 24556447]

Arsenault 2013
Arsenault KA, Yusuf AM, Crystal E, Healey JS, Morillo CA, Nair GM, et al. Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery. *Cochrane Database of Systematic Reviews* 2013, Issue 1. [DOI: 10.1002/14651858.CD003611.pub3; PUBMED: 23440790]

Ashor 2014
Ashor AW, Lara J, Mathers JC, Siervo M. Effect of vitamin C on endothelial function in health and disease: a systematic review and meta-analysis of randomised controlled trials. *Atherosclerosis* 2012;**235**(1):9–20. [DOI: 10.1016/j.atherosclerosis.2014.04.004; PUBMED: 24792921]

Ashton 1999
Ashton T, Young IS, Peters JR, Jones E, Jackson SK, Davies B, et al. Electron spin resonance spectroscopy, exercise, and oxidative stress: an ascorbic acid intervention study. *Journal of Applied Physiology* 1999;**87**(6):2032–6. [PUBMED: 10601146]

Ballmer 1994
Ballmer PE, Reinhart WH, Jordan P, Buhler E, Moser UK, Gey KF. Depletion of plasma vitamin C but not of vitamin E in response to cardiac operations [correction in 1995;110 (4):1972]. *Journal of Thoracic and Cardiovascular Surgery* 1994;**108**(2):311–20. [PUBMED: 8041179]

Berger 2015
Berger MM, Oudemans-van Straaten HM. Vitamin C supplementation in the critically ill patient. *Current Opinion in Clinical Nutrition and Metabolic Care* 2015;**18** (2):193–201. [DOI: 10.1097/MCO.0000000000000148; PUBMED: 25635594]

Bhave 2012
Bhave PD, Goldman LE, Vittinghoff E, Maselli J, Auerbach A. Incidence, predictors, and outcomes associated with postoperative atrial fibrillation after major noncardiac surgery. *American Heart Journal* 2012;**164**(6):918–24. [DOI: 10.1016/j.ahj.2012.09.004; PUBMED: 23194493]

Borelli 1996
Borrelli E, Roux-Lombard P, Grau GE, Girardin E, Ricou B, Dayer J, et al. Plasma concentrations of cytokines, their soluble receptors, and antioxidant vitamins can predict the development of multiple organ failure in patients at risk. *Critical Care Medicine* 1996;**24**(3):392–7. [PUBMED: 8625625]

Carpenter 1986
Carpenter KJ. *The History of Scurvy and Vitamin C*. Cambridge: Cambridge University Press, 1986.

Cathcart 1981
Cathcart RF. Vitamin C, titrating to bowel tolerance, anascorbemia, and acute induced scurvy. *Medical Hypotheses* 1981;**7**(11):1359–76. [DOI: 10.1016/0306-9877%2881%2990126-2%22%3Ehttp://dx.doi.org/10.1016/0306-9877(81)90126-2; PUBMED: 7321921]

Churg 2014
Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014;**129**(8):837–47. [DOI: 10.1161/CIRCULATIONAHA.113.005119; PUBMED: 24345399]

Collier 2008
Collier BR, Giladi A, Dossett LA, Dyer L, Fleming SB, Cotton BA. Impact of high-dose antioxidants on outcomes in acutely injured patients [comment in: 2009;33(4):447-8]. *JPEN. Journal of Parenteral and Enteral Nutrition* 2008; **32**(4):384–8. [DOI: 10.1177/0148607108319808; DOI: 10.1177/0148607108328520; PUBMED: 18596309; PUBMED: 19229041]

Cook 2007
Cook NR, Albert CM, Gaziano JM, Zaharris E, MacFadyen J, Danielson E, et al. A randomized factorial trial of vitamins C and E and beta carotene in the secondary prevention of cardiovascular events in women: results from the Women's Antioxidant Cardiovascular Study. *Archives of Internal Medicine* 2007;**167**(15):1610–8. [DOI: 10.1001/archinte.167.15.1610; PUBMED: 17698683]

Dai 2009
Dai DF, Rabinovitch PS. Cardiac aging in mice and humans: the role of mitochondrial oxidative stress. *Trends in Cardiovascular Medicine* 2009;**19**(7):213–20. [DOI: 10.1016/j.tcm.2009.12.004; PUBMED: 20382344]

De Vecchi 1998
De Vecchi E, Pala MG, Di Credico G, Agape V, Paolini G, Bonini PA, et al. Relation between left ventricular function and oxidative stress in patients undergoing bypass surgery. *Heart* 1998;**79**(3):242–7. [DOI: 10.1136/hrt.79.3.242; PUBMED: 9602656]

Dudley 2005
Dudley SC Jr, Hoch NE, McCann LA, Honeycutt C, Diamandopoulos L, Fukai T, et al. Atrial fibrillation increases production of superoxide by the left atrium and left atrial appendage: role of the NADPH and xanthine oxidases. *Circulation* 2005;**112**(9):1266–73. [DOI: 10.1161/

%E2%80%8BCIRCULATIONAHA.105.538108; PUBMED: 16129811]

Fagerland 2015
Fagerland MW, Lydersen S, Laake P. Recommended confidence intervals for two independent binomial proportions. *Statistical Methods in Medical Research* 2015; **24**(2):224–54. [DOI: 10.1177/0962280211415469; PUBMED: 21996567]

Flowers 2015
Flowers N, Wheelhouse R, Ghannam O, Hartley L, Stranges S, Rees K. Vitamin C supplementation for the primary prevention of cardiovascular disease. *Cochrane Database of Systematic Reviews* 2014, Issue 5. [DOI: 10.1002/14651858.CD011114]

Fogarty 2003
Fogarty A, Lewis SA, Scrivener SL, Antoniak M, Pacey S, Pringle M, Britton J. Oral magnesium and vitamin C supplements in asthma: a parallel group randomized placebo-controlled trial. *Clinical and Experimental Allergy* 2003;**33**(10):1355–9. [DOI: 10.1046/j.1365-2222.2003.01777.x; PUBMED: 14519140]

Galley 1996
Galley HF, Davies MJ, Webster NR. Ascorbyl radical formation in patients with sepsis: effect of ascorbate loading. *Free Radicals in Biology and Medicine* 1996;**20**(1):139–43. [DOI: 10.1016/0891-5849(95)02022-5; PUBMED: 8903690]

Gare 2002
Gare M, Mraovic B, Kehl F, Kersten JR, Warltier DC, Pagel PS. Reactive oxygen species contribute to contractile dysfunction following rapid ventricular pacing in dogs. *International Journal of Cardiology* 2002;**83**(2):125–31. [DOI: 10.1016/S0167-5273(02)00030-X; PUBMED: 12007684]

Go 2001
Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001;**285**(18):2370–5. [DOI: 10.1001/jama.285.18.2370; PUBMED: 11343485]

Harling 2011
Harling L, Rasoli S, Vecht JA, Ashrafian H, Kourliouros A, Athanasiou T. Do antioxidant vitamins have an anti-arrhythmic effect following cardiac surgery? A meta-analysis of randomised controlled trials. *Heart* 2011;**97**(20):1636–42. [DOI: 10.1136/heartjnl-2011-300245; PUBMED: 21865202]

Hathcock 2005
Hathcock JN, Azzi A, Blumberg J, Blumberg J, Bray T, Dickinson A, et al. Vitamins E and C are safe across a broad range of intakes. *American Journal of Clinical Nutrition* 2005;**81**(4):736–45. [: http://ajcn.nutrition.org/content/81/4/736; PUBMED: 15817846]

Hemilä 1997
Hemilä H. Vitamin C intake and susceptibility to the common cold [discussion: 1997;78:857-66]. *British Journal of Nutrition* 1997;**77**:59–72. [DOI: 10.1017/S0007114500002889; PUBMED: 9059230]

Hemilä 2006
Hemilä H. Do vitamins C and E affect respiratory infections? [Dissertation]. University of Helsinki, Helsinki, Finland 2006:6-7, 20-1, 62-3. [: http://hdl.handle.net/10138/20335; : https://oa.doria.fi/handle/10024/1540]

Hemilä 2008
Hemilä H. Vitamin C and sex differences in respiratory tract infections. *Respiratory Medicine* 2008;**102**:625–6. [DOI: 10.1016/j.rmed.2007.12.011; PUBMED: 18222682]

Hemilä 2009a
Hemilä H, Kaprio J. Modification of the effect of vitamin E supplementation on the mortality of male smokers by age and dietary vitamin C. *American Journal of Epidemiology* 2009;**169**(8):946–53. [DOI: 10.1093/aje/kwn413; PUBMED: 19218294]

Hemilä 2009b
Hemilä H. Spectacular reduction in the mortality of acutely injured patients by the administration of vitamins C and E and selenium [letter]. *Journal of Parenteral and Enteral Nutrition* 2009;**33**(4):447–8. [DOI: 10.1177/0148607108328520; PUBMED: 19229041]

Hemilä 2011
Hemilä H, Kaprio J. Vitamin E may affect the life expectancy of men, depending on dietary vitamin C intake and smoking. *Age and Ageing* 2011;**40**(2):215–20. [DOI: 10.1093/ageing/afq178; PUBMED: 21242192]

Hemilä 2013a
Hemilä H, Chalker E. Vitamin C for preventing and treating the common cold. *Cochrane Database of Systematic Reviews* 2013, Issue 1. [DOI: 10.1002/14651858.CD000980.pub4; PUBMED: 23440782]

Hemilä 2013b
Hemilä H, Louhiala P. Vitamin C for preventing and treating pneumonia. *Cochrane Database of Systematic Reviews* 2013, Issue 8. [DOI: 10.1002/14651858.CD005532.pub3]

Hemilä 2014
Hemilä H. The effect of vitamin C on bronchoconstriction and respiratory symptoms caused by exercise: a review and statistical analysis. *Allergy, Asthma & Clinical Immunology* 2014;**10**:58. [DOI: 10.1186/1710-1492-10-58; PUBMED: 25788952]

Higgins 2003
Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. *BMJ* 2003; **327**(7414):557–60. [DOI: 10.1136/bmj.327.7414.557; PUBMED: 12958120]

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1 [updated

March 2011]. The Cochrane Collaboration, 2011. Available at www.cochrane-handbook.org.

Hogue 2005

Hogue CW Jr, Creswell LL, Gutterman DD, Fleisher LA, American College of Chest Physicians. Epidemiology, mechanisms, and risks: American College of Chest Physicians guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery. *Chest* 2005;**128**(2 Suppl):9S–16S. [DOI: 10.1378/chest.128.2˙suppl.9S; PUBMED: 16167659]

Holley 2011

Holley AD, Osland E, Barnes J, Krishnan A, Fraser JF. Scurvy: historically a plague of the sailor that remains a consideration in the modern intensive care unit. *Internal Medicine Journal* 2011;**41**(3):283–5. [DOI: 10.1111/j.1445-5994.2010.02413.x; PUBMED: 21426466]

Hrobjartsson 2010

Hrobjartsson A, Gotzsche PC. Placebo interventions for all clinical conditions. *Cochrane Database of Systematic Reviews* 2010, Issue 1. [DOI: 10.1002/14651858.CD003974.pub3]

Hume 1973

Hume R, Weyers E. Changes in leucocyte ascorbic acid during the common cold. *Scottish Medical Journal* 1973;**18**(1):3–7. [PUBMED: 4717661]

Ide 1999

Ide T, Tsutsui H, Kinugawa S, Utsumi H, Kang D, Hattori N, et al. Mitochondrial electron transport complex I is a potential source of oxygen free radicals in the failing myocardium. *Circulatory Research* 1999;**85**(4):357–63. [DOI: 10.1161/01.RES.85.4.357; PUBMED: 10455064]

Ide 2000

Ide T, Tsutsui H, Kinugawa S, Suematsu N, Hayashidani S, Ichikawa K, et al. Direct evidence for increased hydroxyl radicals originating from superoxide in the failing myocardium. *Circulatory Research* 2000;**86**(2):152–7. [DOI: 10.1161/01.RES.86.2.152; PUBMED: 10666410]

Ioannidis 2007

Ioannidis JP, Trikalinos TA. The appropriateness of asymmetry tests for publication bias in meta-analyses: a large survey. *CMAJ : Canadian Medical Association Journal* 2007;**176**(8):1091–6. [DOI: 10.1503/cmaj.060410; PUBMED: 17420491]

IOM 2000

Institute of Medicine. Vitamin C. *Dietary reference intakes for vitamin C, vitamin E, selenium and carotenoids*. Washington DC: National Academy Press, 2000:95–185. [: http://www.nap.edu/openbook.php?record˙id=9810&page=95]

Iqbal 2005

Iqbal MB, Taneja AK, Lip GY, Flather M. Recent developments in atrial fibrillation. *BMJ* 2005;**330**(7485):238–43. [DOI: 10.1136/bmj.330.7485.238; PUBMED: 15677659]

Jabre 2011

Jabre P, Jouven X, Adnet F, Thabut G, Bielinski SJ, Weston SA, et al. Atrial fibrillation and death after myocardial infarction: a community study. *Circulation* 2011;**123**(19):2094–100. [DOI: 10.1016/j.resuscitation.2011.04.026; PUBMED: 21536994]

Juraschek 2012

Juraschek SP, Guallar E, Appel LJ, Miller ER 3rd. Effects of vitamin C supplementation on blood pressure: a meta-analysis of randomized controlled trials. *American Journal of Clinical Nutrition* 2012;**95**(5):1079–88. [DOI: 10.3945/ajcn.111.027995; PUBMED: 22492364]

Kannel 1998

Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *American Journal of Cardiology* 1998;**82**(8A):2N–9N. [DOI: 10.1016/S0002-9149(98)00583-9; PUBMED: 9809895]

Kim 2003

Kim YH, Lim DS, Lee JH, Shim WJ, Ro YM, Park GH, et al. Gene expression profiling of oxidative stress on atrial fibrillation in humans. *Experimental and Molecular Medicine* 2003;**35**(5):336–49. [DOI: 10.1038/emm.2003.45; PUBMED: 14646586]

Kim 2005

Kim YM, Guzik TJ, Zhang YH, Zhang MH, Kattach H, Ratnatunga C, et al. A myocardial Nox2 containing NAD(P)H oxidase contributes to oxidative stress in human atrial fibrillation. *Circulatory Research* 2005;**97**(7):629–36. [DOI: 10.1161/01.RES.0000183735.09871.61; PUBMED: 16123335]

Kim 2008

Kim YM, Kattach H, Ratnatunga C, Pillai R, Channon KM, Casadei B. Association of atrial nicotinamide adenine dinucleotide phosphate oxidase activity with the development of atrial fibrillation after cardiac surgery. *Journal of the American College of Cardiology* 2008;**51**(1):68–74. [DOI: 10.1016/j.jacc.2007.07.085; PUBMED: 18174039]

Kirsch 2000

Kirsch M, de Groot H. Ascorbate is a potent antioxidant against peroxynitrite-induced oxidation reactions. Evidence that ascorbate acts by re-reducing substrate radicals produced by peroxynitrite. *Journal of Biological Chemistry* 2000;**275**(22):16702–8. [DOI: 10.1074/jbc.M909228199; PUBMED: 10748119]

Korantzopoulos 2007

Korantzopoulos P, Kolettis TM, Galaris D, Goudevenos JA. The role of oxidative stress in the pathogenesis and perpetuation of atrial fibrillation. *International Journal of Cardiology* 2007;**115**(2):135–43. [DOI: 10.1016/j.ijcard.2006.04.026; PUBMED: 16764958]

Kozlowski 2009

Kozlowski D, Budrejko S, Lip GY, Rysz J, Mikhailidis DP, Raczak G, Banach M. Lone atrial fibrillation: what do

we know?. *Heart* 2010;**96**(7):498–503. [DOI: 10.1136/hrt.2009.176321; PUBMED: 19713203]

Lau 2006

Lau J, Ioannidis JP, Terrin N, Schmid CH, Olkin I. The case of the misleading funnel plot. *BMJ* 2006;**333**(7568): 597–600. [DOI: 10.1136/bmj.333.7568.597; PUBMED: 16974018]

Levine 1999

Levine M, Rumsey SC, Daruwala R, Park JB, Wang Y. Criteria and recommendations for vitamin C intake. *JAMA* 1999;**281**(15):1415–23. [DOI: 10.1001/jama.281.15.1415; PUBMED: 10217058]

Levy 2004

Levy D, Kannel WB. Postoperative atrial fibrillation and mortality: do the risks merit changes in clinical practice? . *Journal of the American College of Cardiology* 2004;**43**(5): 749–51. [DOI: 10.1016/j.jacc.2003.12.011; PUBMED: 14998611]

Lip 2012

Lip GY, Tse HF, Lane DA. Atrial fibrillation. *Lancet* 2012;**379**(9816):648–61. [DOI: 10.1016/S0140-6736(11)61514-6; PUBMED: 22166900]

Long 2003

Long CL, Maull KI, Krishnan RS, Laws HL, Geiger JW, Borghesi L, et al. Ascorbic acid dynamics in the seriously ill and injured. *Journal of Surgical Research* 2003;**109**(2):144–8. [DOI: 10.1016/S0022-4804(02)00083-5; PUBMED: 12643856]

May 2013

May JM, Harrison FE. Role of vitamin C in the function of the vascular endothelium. *Antioxidants and Redox Signaling* 2013;**19**(17):2068–83. [DOI: 10.1089/ars.2013.5205; PUBMED: 23581713]

Merchant 2004

Merchant AT, Curhan G, Bendich A, Singh VN, Willett WC, Fawzi WW. Vitamin intake is not associated with community-acquired pneumonia in US men. *Journal of Nutrition* 2004;**134**(2):439–44. [: http://jn.nutrition.org/content/134/2/439; PUBMED: 14747686]

Mihm 2001

Mihm MJ, Yu F, Carnes CA, Reiser PJ, McCarthy PM, Van Wagoner DR, et al. Impaired myofibrillar energetics and oxidative injury during human atrial fibrillation. *Circulation* 2001;**104**(2):174–80. [DOI: 10.1161/01.CIR.104.2.174; PUBMED: 11447082]

Mochalkin 1970

Mochalkin NI. Ascorbic acid in the complex therapy of acute pneumonia. *Voenno-Meditsinskii Zhurnal* 1970;**9**(Sep):17–21. [: translation http://www.mv.helsinki.fi/home/hemila/T5.pdf; PUBMED: 5515787]

Montezano 2012

Montezano AC, Touyz RM. Oxidative stress, Noxs, and hypertension: experimental evidence and clinical controversies [erratum: 44(8):854-8]. *Annals of Medicine* 2012;**44**(Suppl 1):S2–S16. [DOI: 10.3109/07853890.2011.653393; PUBMED: 22713144]

Morita 2009

Morita N, Sovari AA, Xie Y, Fishbein MC, Mandel WJ, Garfinkel A, et al. Increased susceptibility of aged hearts to ventricular fibrillation during oxidative stress. *American Journal of Physiology: Heart and Circulatory Physiology* 2009;**297**(5):H1594–605. [DOI: 10.1152/ajpheart.00579; PUBMED: 19767530]

Mosdøl 2008

Mosdøl A, Erens B, Brunner EJ. Estimated prevalence and predictors of vitamin C deficiency within UK's low-income population. *Journal of Public Health* 2008;**30**(4):456–60. [DOI: 10.1093/pubmed/fdn076; PUBMED: 18812436]

Nathens 2002

Nathens AB, Neff MJ, Jurkovich GJ, Klotz P, Farver K, Ruzinski JT, et al. Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients. *Annals of Surgery* 2002;**236**(6):814–22. [: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1422648/; PUBMED: 12454520]

Neuman 2007

Neuman RB, Bloom HL, Shukrullah I, Darrow LA, Kleinbaum D, Jones DP, et al. Oxidative stress markers are associated with persistent atrial fibrillation. *Clinical Chemistry* 2007;**53**(9):1652–7. [DOI: 10.1373/clinchem.2006.083923; PUBMED: 17599958]

Nishikimi 1975

Nishikimi M. Oxidation of ascorbic acid with superoxide anion generated by the xanthine-xanthine oxidase system. *Biochemical and Biophysical Research Communications* 1975;**63**(2):463–8. [DOI: 10.1016/0006-291X(75)90710-X; PUBMED: 235924]

Padayatty 2004

Padayatty SJ, Sun H, Wang Y, Riordan HD, Hewitt SM, Katz A, et al. Vitamin C pharmacokinetics: implications for oral and intravenous use. *Annals of Internal Medicine* 2004;**140**(7):533–7. [DOI: 10.7326/0003-4819-140-7-200404060-00010; PUBMED: 15068981]

Padayatty 2010

Padayatty SJ, Sun AY, Chen Q, Espey MG, Drisko J, Levine M. Vitamin C: intravenous use by complementary and alternative medicine practitioners and adverse effects. *PLoS One* 2010;**5**(7):e11414. [DOI: 10.1371/journal.pone.0011414; PUBMED: 20628650]

Padayatty 2014

Padayatty SJ, Levine M. Vitamin and mineral supplements in the primary prevention of cardiovascular disease and cancer [letter]. *Annals of Internal Medicine* 2014;**160**(9): 654. [DOI: 10.7326/L14-5009; PUBMED: 24798530]

Page 2004

Page RL. Newly diagnosed atrial fibrillation. *New England Journal of Medicine* 2004;**351**(23):2408–16. [DOI: 10.1056/NEJMcp041956; PUBMED: 15575057]

Panagiotou 2013

Panagiotou OA, Contopoulos-Ioannidis DG, Ioannidis JP. Comparative effect sizes in randomised trials from

less developed and more developed countries: meta-epidemiological assessment. *BMJ* 2013;**346**:f707. [DOI: 10.1136/bmj.f707; PUBMED: 23403829]

Perk 2012

Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). *European Heart Journal* 2012;**33**(13):1635–701. [DOI: 10.1093/eurheartj/ehs092; PUBMED: 22555213]

Powers 2011

Powers SK, Nelson WB, Hudson MB. Exercise-induced oxidative stress in humans: cause and consequences. *Free Radicals in Biology and Medicine* 2011;**51**(5):942–50. [DOI: 10.1016/j.freeradbiomed.2010.12.009; PUBMED: 21167935]

R-Project 2015

http://www.r-project.org/. The R Project for Statistical Computing. http://www.r–project.org/, 2015.

Raynaud-Simon 2010

Raynaud-Simon A, Cohen-Bittan J, Gouronnec A, Pautas E, Senet P, Verny M, et al. Scurvy in hospitalized elderly patients. *Journal of Nutrition, Health and Aging* 2010;**14**(6): 407–10. [DOI: 10.1007/s12603-010-0032-y; PUBMED: 20617280]

RevMan 2012

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

Rice 2000

Rice ME. Ascorbate regulation and its neuroprotective role in the brain. *Trends in Neurological Sciences* 2000; **23**:209–16. [DOI: 10.1016/S0166-2236(99)01543-X; PUBMED: 10782126]

Rodemeister 2014

Rodemeister S, Duquesne M, Adolph M, Nohr D, Biesalski HK, Unertl K. Massive and long-lasting decrease in vitamin C plasma levels as a consequence of extracorporeal circulation. *Nutrition* 2014;**30**(6):673–8. [DOI: 10.1016/j.nut.2013.10.026; PUBMED: 24631388]

Rümelin 2005

Rümelin A, Humbert T, Luhker O, Drescher A, Fauth U. Metabolic clearance of the antioxidant ascorbic acid in surgical patients. *Journal of Surgical Research* 2005;**129** (1):46–51. [DOI: 10.1016/j.jss.2005.03.017; PUBMED: 16085104]

Schleicher 2009

Schleicher RL, Carroll MD, Ford ES, Lacher DA. Serum vitamin C and the prevalence of vitamin C deficiency in the United States: 2003-2004 National Health and Nutrition Examination Survey (NHANES). *American Journal of Clinical Nutrition* 2009;**90**(5):1252–63. [DOI: 10.3945/ajcn.2008.27016; PUBMED: 19675106]

Schorah 1996

Schorah CJ, Downing C, Piripitsi A, Gallivan L, Al-Hazaa AH, Sanderson MJ, et al. Total vitamin C, ascorbic acid, and dehydroascorbic acid concentrations in plasma of critically ill patients. *American Journal of Clinical Nutrition* 1996;**63**(5):760–5. [: http://ajcn.nutrition.org/content/63/5/760; PUBMED: 8615361]

Sesso 2008

Sesso HD, Buring JE, Christen WG, Kurth T, Belanger C, MacFadyen J, et al. Vitamins E and C in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. *JAMA* 2008;**300**(18): 2123–33. [DOI: 10.1001/jama.2008.600; PUBMED: 18997197]

Shite 2001

Shite J, Qin F, Mao W, Kawai H, Stevens SY, Liang C. Antioxidant vitamins attenuate oxidative stress and cardiac dysfunction in tachycardia-induced cardiomyopathy. *Journal of the American College of Cardiology* 2001;**38** (6):1734–40. [DOI: 10.1016/S0735-1097(01)01596-0; PUBMED: 11704389]

Silvestro 2002

Silvestro A, Scopacasa F, Oliva G, de Cristofaro T, Iuliano L, Brevetti G. Vitamin C prevents endothelial dysfunction induced by acute exercise in patients with intermittent claudication. *Atherosclerosis* 2002;**165**(2):277–83. [DOI: 10.1016/S0021-9150(02)00235-6; PUBMED: 12417278]

Smith 2011

Smith A, Di Primio G, Humphrey-Murto S. Scurvy in the developed world. *CMAJ : Canadian Medical Association Journal* 2011;**183**(11):E752–2. [DOI: 10.1503/cmaj.091938; PUBMED: 21555388]

Sterne 2011

Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;**343**:d4002. [DOI: 10.1136/bmj.d4002; PUBMED: 21784880]

Talkhabi 2015

Talkhabi M, Pahlavan S, Aghdami N, Baharvand H. Ascorbic acid promotes the direct conversion of mouse fibroblasts into beating cardiomyocytes. *Biochemical and biophysical research communications* 2015;**463**(4): 699–705. [DOI: 10.1016/j.bbrc.2015.05.127; PUBMED: 26047705]

Tanaka 2000

Tanaka H, Matsuda T, Miyagantani Y, Yukioka T, Matsuda H, Shimazaki S. Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid administration: a randomized, prospective study. *Archives of Surgery* 2000; **135**(3):326–31. [DOI: 10.1001/archsurg.135.3.326; PUBMED: 10722036]

Terrin 2005

Terrin N, Schmid CH, Lau J. In an empirical evaluation of the funnel plot, researchers could not visually identify publication bias. *Journal of Clinical Epidemiology* 2005; **58**(9):894–901. [DOI: 10.1016/j.jclinepi.2005.01.006; PUBMED: 16085192]

Toroser 2007

Toroser D, Sohal RS. Age-associated perturbations in glutathione synthesis in mouse liver. *Biochemical Journal* 2007;**405**(3):583–9. [DOI: 10.1042/BJ20061868; PUBMED: 17461778]

Turagam 2012

Turagam MK, Velagapudi P, Kocheril AG. Atrial fibrillation in athletes. *American Journal of Cardiology* 2012;**109** (2):296–302. [DOI: 10.1016/j.amjcard.2011.08.041; PUBMED: 22019138]

Van Wagoner 2008

Van Wagoner DR. Oxidative stress and inflammation in atrial fibrillation: role in pathogenesis and potential as a therapeutic target. *Journal of Cardiovascular Pharmacology* 2008;**52**(4):306–13. [DOI: 10.1097/FJC.0b013e31817f9398; PUBMED: 18791466]

Violi 2014

Violi F, Pastori D, Pignatelli P, Loffredo L. 29.Antioxidants for prevention of atrial fibrillation: a potentially useful future therapeutic approach? A review of the literature and meta-analysis. *Europace* 2014;**16**(8):1107–16. [DOI: 10.1093/europace/euu040; PUBMED: 24706090]

Wang 2003

Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation* 2003;**107**(23): 2920–4. [DOI: 10.1161/01.CIR.0000072767.89944.6E; PUBMED: 12771006]

Wang 2013

Wang Y, Liu XJ, Robitaille L, Eintracht S, MacNamara E, Hoffer LJ. Effects of vitamin C and vitamin D administration on mood and distress in acutely hospitalized patients. *American Journal of clinical Nutrition* 2013;**98**(3): 705–11. [DOI: 10.3945/ajcn.112.056366; PUBMED: 23885048]

WB 2015

World Bank. GDP per capita (current US$). http://data.worldbank.org/indicator/NY.GDP.PCAP.CD 2015.

Wyse 2004

Wyse DG. Overview of endpoints in atrial fibrillation studies. *Heart Rhythm* 2004;**1**(2 Suppl):B3–7. [DOI: 10.1016/j.hrthm.2004.03.070; PUBMED: 15851133]

Zhang 2011

Zhang M, Robitaille L, Eintracht S, Hoffer LJ. Vitamin C provision improves mood in acutely hospitalized patients. *Nutrition* 2011;**27**(5):530–3. [DOI: 10.1016/j.nut.2010.05.016; PUBMED: 20688474]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bjordahl 2012

Methods	Randomised placebo-controlled secondary prevention trial.
Participants	USA, CABG patients, 124 M / 61 F; mean 63 yr (SD 12 yr); 89 vit C / 96 placebo **Inclusion:** >18 yr who were scheduled to undergo CABG. **Exclusion:** current AF, temporary or permanent pacemaker, life expectancy <1 month, emergency surgery precluding the initiation of study protocol the evening before surgery, current pregnancy
Interventions	**Vit C before the operation:** **Dose:** 2 g **Method:** po **Timing:** "evening before surgery" **Vit C after operation:** **Dose:** 2 g/d **Method:** po **Duration:** 5 d. **Placebo:** identical placebo capsules at the same intervals; the inert substance for both treatment and placebo capsules was talc
Outcomes	POAF (Analysis 1.1) "Postoperative AF or atrial flutter for 10 minutes" (p 863), Length of hospital stay (Analysis 2.1), Length of ICU stay (Analysis 3.1), Length of mechanical ventilation (Analysis 4.1).
Notes	The authors reported the length of ventilation time as 1.2 (SD 0.8) days in vitamin C group and 1.4 (SD 1) days in the placebo group. With the RevMan program, this gives P = 0.13, whereas the authors published P = 0.032. We adjusted to SD = 0.632 days to both groups which leads to P = 0.032 in RevMan We received no reply to our emails asking for more details.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Enrolled participants were randomized to either ... The pharmacy department maintained the randomization list ..." (p 863).
Allocation concealment (selection bias)	Low risk	"The pharmacy department maintained the randomization list and assigned participants to the placebo and treatment arms of the study in a blinded fashion. Participants,

Bjordahl 2012 (*Continued*)

		clinicians, and evaluators were blinded to the treatment assignments and the blind was not broken until after data analyses were complete" (p 863)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	See above.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	13 participants were withdrawn from analysis because of surgery postponement/cancellation, presence of exclusion criteria at the time of enrollment etc
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	"Both ascorbic acid and inert placebo capsules were prepared by a custom pharmacy" (p 863) indicates that the products were not commercial

Colby 2011

Methods	Randomised placebo-controlled secondary prevention trial.
Participants	USA, CABG and valvular surgery patients, 19 M / 5 F, mean 65 yr (SD 9 yr), 13 vit C / 11 placebo **Inclusion:** >18 yr who were scheduled to undergo CABG, valvular surgery, or both **Exclusion:** excluded if they were pregnant or had a history of renal calculi
Interventions	**Vit C before the operation:** **Dose:** 2 g **Method:** po **Timing:** "night before surgery" **Vit C after operation:** **Dose:** 1 g/d **Method:** po **Duration:** 5 d. **Placebo:** Both vit C and placebo were placed into identical capsules to allow for double-blinding
Outcomes	POAF (Analysis 1.1) "Post-CTS AF, defined as any documented AF of more than five minutes' duration occurring between the day of surgery and postoperative day 4" (p 1633),

Colby 2011 (*Continued*)

	Length of hospital stay (Analysis 2.1), Length of ICU stay (Analysis 3.1).	
Notes	No reply to our emails.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"... randomized using a computer-generated sequence with a 1:1 allocation and a random block size of 10" (p 1633)
Allocation concealment (selection bias)	Low risk	"Study patients, cardiothoracic surgeons, caregivers, and investigators, including those responsible for data collection, were blinded to the treatment allocation" (p 1633)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	See above.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient "suffered a ventricular arrhythmia before undergoing cardiothoracic surgery and was excluded" (p 1634)
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Dehghani 2014

Methods	Randomised secondary prevention trial.
Participants	Iran, CABG patients, 74 M / 26 F, mean 61 yr (SD 7 yr); 50 vit C / 50 control **Inclusion:** Patients who underwent elective isolated on-pump CABG surgery, age >50 yr, no history of CABG surgery, taking beta-blocker before and after surgery **Exclusion:** history of any cardiac arrhythmia and/or being under anti-arrhythmic therapy, being under digoxin therapy, having pacemaker, severe CHF and/or LVEF <30%, renal failure, severe hepatic failure, COPD, no occurrence of intra- or post-operative cardiopulmonary arrest, or any degree of cardiac blockade and/or bradycardia

Interventions	**Vit C before the operation:** **Dose:** 2 g **Method:** po **Timing:** "All patients took the tablets within 12 hours before surgery" (email 2015-9-9) **Vit C after operation:** **Dose:** 1 g/d **Method:** po **Duration:** 5 d. **Placebo:** No formal placebo, but the patients received many drugs and it is unlikely that they identified vitamin C among all the other administered drugs. We classify that all the other drugs serve as a functional placebo to vitamin C
Outcomes	POAF (Analysis 1.1) "Postoperative AF was defined as patients who had an episode of AF lasting more than 10 min" [length of the follow-up 5 d] (p 494), Length of hospital stay (Analysis 2.1), Length of ICU stay (Analysis 3.1).
Notes	Additional information was received by emails from Yousef Rezaei on 2015-4-11, 2015-4-22, 2015-9-9, see above and below

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"All patients were randomized into two groups in a 1:1 ratio using random-number table" (p 493)
Allocation concealment (selection bias)	Low risk	"Neither ward physician nor Holter interpreter were aware of the patients' group. Only one who analyzed data was aware of the patients' group" (email 2015-4-11) and "we did not let ward physician and surgeons to know which of patients taking vitamin c or not, except for being informed about the conduction of our trial and prescribing some of patients to take vitamin c. Furthermore, patients were informed that they would be included in our trial to be prescribed vitamin c" (email 2015-4-22)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	See above. Placebo was not used. Therefore in our sensitivity analyses we exclude the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above.

Dehghani 2014 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	"There was no patient withdrawal or missing during study. All allocated ones completed study" (email 2015-4-11 and 2015-10-1)
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	"Our study was funded by Urmia University of Medical Sciences, Iran." (email 2015-10-1)

Donovan 2012

Methods	Randomised placebo-controlled 2x2 factorial study with vitamin C and amiodarone
Participants	USA, 300 **Inclusion:** >18 yr, comers for elective or urgent open heart surgery (CABG, Valve repair or replacement, Combined CABG/Valves, CABG/other, Other) **Exclusion:** history of AF, emergency surgery, contraindications to study medications, untreated thyroid disease, hepatic failure, pregnancy
Interventions	**Vit C before the operation:** **Dose:** 2 g/d **Method:** po **Timing:** 2 g "evening before surgery" and 2 g "morning of surgery" **Vit C after operation:** **Dose:** 2 g/d **Method:** po **Duration:** 5 d **Placebo:** was used, but no details
Outcomes	POAF, length of hospital stay. length of ICU stay. Unfortunately we were unable to get data for these outcomes
Notes	This was identified from ClinicalTrials.gov, but there are no data available about participants or results We were able to contact Dr. Kramer (email 2015-9-9) who gave additional information It is possible we will get the results, but we did not get them in time for the deadline of this submission. We will add them later, if we get them

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Allocation: Randomized
Allocation concealment (selection bias)	Low risk	Masking: Double Blind (Investigator, Outcomes Assessor)

Donovan 2012 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Masking: Double Blind (Investigator, Outcomes Assessor)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Masking: Double Blind (Investigator, Outcomes Assessor)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	?
Selective reporting (reporting bias)	Unclear risk	?
Other bias	Unclear risk	?

Eslami 2007

Methods	Randomised secondary prevention trial.
Participants	Iran, CABG patients, 67 M / 33 F, mean 60 yr (SD 7 yr), 50 vit C / 50 control **Inclusion:** Isolated CABG patients with age >50 yr and treatment with beta-blockers for a target heart rate of about 60-70 bpm, at least 1 week before surgery **Exclusion:** a history of AF, medication with class I and III antiarrhythmic agents or digoxin, a permanent or temporary pacemaker, any degree of AV block or bradycardia, end stage renal disease, severe pulmonary disease, severe hepatic disease
Interventions	**Vit C before the operation:** **Dose:** 2 g **Method:** po **Timing:** "night before surgery" **Vit C after operation:** **Dose:** 2 g/d **Method:** po **Duration:** 5 d. **Placebo:** No formal placebo, but the patients received many medicines and it is unlikely that they identified vitamin C among all the other administered drugs, see below. We classify that all the other drugs serve as a functional placebo to vitamin C
Outcomes	POAF (Analysis 1.1) "An episode of atrial fibrillation lasting >10 minutes or the requirement for urgent intervention due to atrial fibrillation" (p 270), Length of hospital stay (Analysis 2.1), Length of ICU stay (Analysis 3.1).
Notes	Additional information was received by email from Mehdi Mousavi on 2015-4-19, see below "The study was performed as a thesis of cardiology degree and it was supported by Tehran University of medical sciences as a survey project" (email)

Eslami 2007 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomized trial"... "patients were randomly assigned to..." (p 269) "The randomization was done with block randomization ... Randomization was done by 1 investigator blinded to the drugs therapy and holter results. It was done with a table of 4 cell block randomization" (email 2015-4-19)
Allocation concealment (selection bias)	Low risk	See above.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The surgeons were blinded. Ascorbic acid prescription and randomization was done by me, blinded to the results of holter and follow up and holter recordings were red by Dr. Eslami who was blinded to everything. .. A patient who is a candidate for cardiac surgery might take many medications, usually including aspirin, nitrates, statins, possibly ACE inhibitors or ARBs etc., and as the design of our study beta blocker prescription was done to both group, thus 2 groups were receiving lots of drugs and including placebo or not including it in the regimen might not have a serious effect on result of holter monitoring that is an objective observation. Other drugs could work as placebo for control group!" (email 2015-4-19) In our authors' judgement, we do not consider that the findings are biased by the lack of formal placebo in the placebo group, but in sensitivity analysis we exclude this study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All of the Holter recordings were examined by a single investigator who had been blinded to patients' group assignments" (p 270)
Incomplete outcome data (attrition bias) All outcomes	Low risk	"There was no drop out. The study was in-hospital and thus we were able to follow all included patients" (email 2015-4-19)
Selective reporting (reporting bias)	Low risk	

Eslami 2007 (*Continued*)

Other bias	Low risk	Funding: "The study was performed as a thesis of cardiology degree and it was supported by Tehran University of medical sciences as a survey project." (email 2015-4-11)

Healy 2010

Methods	Randomised secondary prevention trial.
Participants	USA, 30 CABG patients; no data of sex and age distributions. **Inclusion:** patients >18yr able to provide informed consent. **Exclusion:** persistent or recent AF, or patients who have taken a class I or III antiarrhythmic agent within a predefined period
Interventions	Vitamin C dosage and duration not reported in the abstract **Placebo:** No placebo. We classify that all the other drugs serve as a functional placebo to vitamin C
Outcomes	POAF (Analysis 1.1). Length of hospital stay was measured (N = 60), but not reported
Notes	Published only as an abstract. No reply to our emails.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Title states that the study was "randomized"
Allocation concealment (selection bias)	Unclear risk	?
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	?
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	?
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	?
Selective reporting (reporting bias)	High risk	Hospital stay measured but not reported

Healy 2010 (*Continued*)

Other bias	Unclear risk	?

Korantzopoulos 2005

Methods	Randomised secondary prevention trial.
Participants	Greece, patients after a successful cardioversion, 26 M / 18 F, mean 68 yr (SD 10 yr); 22 vit C / 22 control. No information about the etiology of AF **Inclusion:** persistent AF (>1 week) scheduled for elective external electrical cardioversion, participants who restored SR for >1 hr were included in the analysis **Exclusion:** thyroid dysfunction, valvular heart disease, left atrial diameter >55 mm, congestive HF (NYHA class >II), recent acute coronary event or revascularization, recent infection, malignancies, WBC dyscrasias, autoimmune or inflammatory diseases, renal failure, or hepatic failure. Patients receiving drugs with antiinflammatory or antioxidant action, apart from statins, as well as multivitamin compounds
Interventions	**Vit C before cardioversion:** **Dose:** 2 g **Method:** po **Timing:** "12 h before cardioversion" **Vit C after operation:** **Dose:** 1 g/d **Method:** po **Duration:** 7 d. Before cardioversion 2 g vit C orally and thereafter 1 g daily for 7 d **Placebo:** No placebo, vitamin C tablets were bought by the patients.
Outcomes	Recurrence of AF after a succesful cardioversion (Analysis 1.1). "Early AF recurrence was defined as relapse into AF within 1 week following successful cardioversion" (p 322)
Notes	Additional information was received by email from Panagiotis Korantzopoulos on 2015-4-11, see below "There was no funding. Vitamin C tablets were bougth by the patients - very cheap tablets" (email 2015-4-11)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomised in one to one fashion" (p 322).
Allocation concealment (selection bias)	Low risk	"Yes we used allocation concealment" (email 2015-4-11).

Korantzopoulos 2005 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"The physician that was responsible for cardioversion and follow-up of each patient was unaware of the treatment that was assigned to the patient" (p 322). However, "Vitamin C tablets were bougth by the patients - very cheap tablets" (email 2015-4-11) In our authors' judgement, we do not consider that the findings are biased by the lack of placebo in the placebo group, but in our sensitivity analysis we exclude this study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above and "All measurements were performed blindly to the patients characteristics and treatment" (p 322)
Incomplete outcome data (attrition bias) All outcomes	Low risk	"In six patients, cardioversion failed to restore sinus rhythm and were excluded from the analysis" (p 322)
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	Funding: "There was no funding. Vitamin C tablets were bought by the patients - very cheap tablets" (email 2015-4-10)

Papoulidis 2011

Methods	Randomised placebo-controlled secondary prevention trial.
Participants	Greece, CABG patients, 120 M / 50 F, mean 73 yr (SD 7 yr); 85 vit C / 85 placebo **Inclusion:** Patients scheduled to undergo elective isolated CABG **Exclusion:** <65 yr, preoperative AF, hyperoxaluria, permanent or temporary pacemaker, severe renal or hepatic failure, medication with class I and III antiarrhythmic agents or digoxin, any degree of AV block or bradycardia with a HR <50 bpm, severe pulmonary disease, enlarged left atrium (LA diameter >4.4 cm)
Interventions	**Vit C before the operation:** **Dose:** 2 g **Method:** iv **Timing:** "3 h prior the initiation of CPB" **Vit C after operation:** **Dose:** 1 g/d **Method:** iv **Duration:** 5 d. **Placebo:** intravenous administration of 0.9% saline. "Same amount and at the same time" (email)

Outcomes	POAF (Analysis 1.1) "The detection of an episode of AF lasting >10 min or the requirement for urgent intervention due to AF" (p 122) "The outcome was monitored till the day of the discharge, usually day 6-7 postop" Length of ICU stay (Analysis 3.1), Length of hospital stay (Analysis 2.1).
Notes	Additional information was received by emails from Pavlos Papoulidis on 2015-5-15 and 2015-6-2, see above and below "It was more like a self funding" (email). The authors reported the length of hospital stay as 7.9 (SD 2.2) days in vitamin C group and 9.8 (SD 3.6) days in the placebo group. With the RevMan program, this gives P < 0.0001, whereas the authors published P = 0.04. We adjusted SD = 6.00 days to both groups which leads to P = 0.04 in RevMan The authors reported the length of ICU stay as 1.6 (SD 0.9) days in vitamin C group and 2.1 (SD 1.1) days in the placebo group. With the RevMan program, this gives P= 0.0014, whereas the authors published P = 0.05. We adjusted SD = 1.66 days to both groups which leads to P = 0.05 in RevMan

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The initial random assignment was by flipping a coin ... to have an equal sample size, we reevaluated our randomization protocol and using a random generator ... " (p 122)
Allocation concealment (selection bias)	Low risk	"During the randomization stage, patients and physicians were not aware of the group to which the participants were allocated" (email 2015-6-2)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"During the study, patients and physicians in charge of the treatment, surgeons carrying out the operation, and the physicians interpreting the ECG recordings were all blinded of the study group" (email 2015-6-2)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) All outcomes	Low risk	"No dropouts/withdrawals" (email 2015-5-15)
Selective reporting (reporting bias)	Low risk	

Other bias	Low risk	Funding: "It was more like a self funding." (email 2015-5-15)

Polymeropoulos 2015

Methods	Randomised placebo-controlled secondary prevention trial.
Participants	Greece, CABG patients, 22 CABG patients; 13 M 9 F; Mean age 70 (range 41 to 85); 11 vit C 11 Placebo **Inclusion Criteria:** Patients undergoing on-pump cardiac surgery **Exclusion Criteria:** off-pump cardiac surgery procedure, AF before the procedure, recent infection and/or infectious endocarditis, neoplasia, chronic renal failure, hepatic failure, autoimmune disease and/or disease that brings about a systematic inflammatory response, thyroid disease, systematic use of supplements that contain vitC or carnitine, use of NSAIDs other than aspirin for a time period up to one month before the procedure
Interventions	**Vit C before the operation:** **Dose:** 2 g/d **Method:** iv **Timing:** "The last dose of vitC was on the evening before" about 12 hours (email 2015-9-9) **Vit C after operation:** **Dose:** 2 g/d **Method:** iv **Duration:** 4 d. **Placebo** was saline
Outcomes	POAF (Analysis 1.1) Length of ICU stay (Analysis 3.1) Length of mechanical ventilation (Analysis 4.1) Data for the latter two outcomes were kindly sent to us by Dr. Polymeropoulos as a data set
Notes	This summary is based on ClinicalTrials.gov document NCT01107730 No full report of the trial was available. Additional information was received by email from Evangelos Polymeropoulos on 2015-9-9 and on 2015-9-16, see above and below

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was performed by permutated blocks." (email 2015-9-9)
Allocation concealment (selection bias)	Low risk	Double-blind implies allocation concealment

Polymeropoulos 2015 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"We did not have any dropouts" (email 2015-9-9)
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Rebrova 2012

Methods	Randomised secondary prevention trial.
Participants	Russia, CABG patients, 40 M / 0 F, mean 59 yr (SD 7 yr); 20 vit C / 20 placebo Patients suffering from chronic IHD. All the patients received standard basic treatment before and after operation, including beta-blockers
Interventions	**Vit C before the operation:** **Dose:** 2 g **Method:** po **Timing:** "evening before the operation" **Vit C after operation:** **Dose:** 2 g/d **Method:** po **Duration:** 5 d. **No placebo**
Outcomes	POAF (Analysis 1.1) "AF was defined by sporadic ECG records when the patient feels the palpitations. There was no the recording of the occurrence of AF limited to 5 days, which is the vitamin C administration period." (email 2015-6-17) "After surgery patients were placed in the department of anesthesiology and intensive care. Certainly, in the intensive care department the patients were recorded ECG. As wrote in our article the control of the arrhythmias was performed by ECG monitoring" (email 2015-6-18)
Notes	Additional information was received by emails from Tatjana Rebrova on 2015-6-17 and 2015-6-18, see above and below We arranged translation of the text to English.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Rebrova 2012 (*Continued*)

Random sequence generation (selection bias)	Low risk	"To separate the patients into groups, we used the method of envelope randomization: 20 sealed envelopes contained a piece of paper with the word 'control group', 20 - the inscription 'core group'. The envelopes were mix in a box, and mixed before each withdrawal next envelope. On a certain day we started this research. After the patient signed an informed consent about participation in this research, our researcher took an envelope out of the box and dissected it." (email 2015-6-17) "The 'core group' is the group of patients which took vitamin C" (email 2015-6-18)
Allocation concealment (selection bias)	Low risk	See above
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"We did not use placebo. Surgeons were informated about to which group patient belonged" (email 2015-6-17) "the patients and all physicians knew which groups the patients belonged" (email 2015-6-18)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See above
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomized were included in analysis
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Sadeghpour 2015

Methods	Randomised placebo-controlled secondary prevention trial.
Participants	Iran, CABG or valvular surgery patients, 191 M / 99 F, mean 56 yr (SD 14 yr); 113 vit C / 177 placebo **Inclusion:** >18 yr with American Society of Anesthesiologists physical status class II-III and candidacy for CABG or simple congenital valvular disease surgery **Exclusion:** who died within the 1st postoperative day and those who had not received adequate doses of drugs according to our protocol, severe complications (cardiac, respiratory or neurological) or emergent operation

Sadeghpour 2015 (*Continued*)

Interventions	**Vit C before the operation:** **Dose:** 2 g **Method:** iv **Timing:** "immediately before surgery" **Vit C after operation:** **Dose:** 1 g/d **Method:** po **Duration:** 4 d. **Placebo:** "The patients in the placebo group received an equal number of identical tablets. The placebo tablets and ampoules were prepared in the same shape and size as the original" (p 2). Before surgery: "The Vit C was given in the operating room along with the other infusions by anesthesiologist technician" (email 2015-5-11)
Outcomes	POAF (Analysis 1.1) "AF rhythm was defined by 10 min period of AF rhythm in the ECG monitoring for the first 3-4th days after the cardiac surgery or when it was detected in 12- lead ECG in day 4 or 5 after the surgery (Continuous ECG monitoring for day 3-4 and daily ECG on day 4 and 5 based on our protocol) or whenever symptoms occurred and was documented by ECG monitoring" and the recording was limited to 5 days (email 2015-5-12), Length of hospital stay (Analysis 2.1), Length of ICU stay (Analysis 3.1).
Notes	Additional information was received by email from Anita Sadeghpour on 2015-5-12 and 2015-10-1, see below and above The authors reported the length of hospital stay as 10.17 (SD 4.63) days in vitamin C group and 12 (SD 4.51) days in the placebo group. With the RevMan program, this gives P < 0.0009, whereas the authors published P = 0.01. We adjusted SD = 5.90 days to both groups which leads to P = 0.01 in RevMan

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The study population was randomized one day before surgery to two groups (By using www.randomaizer.org) ... The method of randomization was balanced block with an allocation sequence based on a block size of eight" (p 2) However, the sizes of the groups 113 vit C / 177 placebo are not consistent with block randomization. Therefore we exclude this study in our sensitivity analysis
Allocation concealment (selection bias)	Low risk	"Both the patients and the hospital staff were blind to the treatment allocation" (p 2)

Sadeghpour 2015 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	See above. "The Vit C was given in the operating room along with the other infusions by anesthesiologist technician" (email 2015-5-12)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	"We paid it by ourselves besides getting help from the Rajaei cardiovascular research center." (email 2015-10-1)

Samadikhah 2014

Methods	Randomised placebo-controlled secondary prevention trial.
Participants	Iran, CABG patients 82 M / 38 F, mean 61 yr (SD 11 yr); 60 vit C / 60 placebo. **Inclusion:** patients who were scheduled to undergo CABG surgery. **Exclusion:** AF, left atrial hypertrophy, heart valve disease, myocardial infarction and ejection fraction of left ventricle <40%
Interventions	**Vit C before the operation:** **Dose:** 2 g **Method:** po **Timing:** "in operation day" **Vit C after operation:** **Dose:** 1 g/d **Method:** po **Duration:** 5 d. **Placebo:** "placebo with the same dose were used for controls" (p 98). "The tablets were prepared by the pharmacy faculty with the size, weight and shape to that of the vit C tablets we used in the study" (email 2015-4-19)
Outcomes	POAF (Analysis 1.1), "AF diagnosis was based on EKG findings (consisting a standard 12 lead EKG with a long lead II)" based on 5-day followup (email 2015-4-19), Length of hospital stay and length of ICU stay were measured and mentioned in the report, but data were not reported, and the data were not available for us, when we contacted Dr. Golzari

Notes	Additional information was received by email from Samad Golzari on 2015-4-19, see below	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"for a random double-blind clinical trial" (p 98); "Randlist software was used" (email 2015-4-19)
Allocation concealment (selection bias)	Low risk	"double blind" (p 98) implies allocation concealment and "yes" (email 2015-4-19) to our question describing the concept of allocation concealment, and whether it was used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double blind" (p 98) and "Patients did not know if the medication they received was vit C or placebo. Neither was the physician giving the medications to the patients aware of the content of the tablets" (email 2015-4-19), and surgeons carrying out the CABG operation, physicians in the ICU, physicians assessing the ECG: "All above mentioned people were blinded as the medication was given by a single person who was also blinded to the medications" (email 2015-4-19)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"there were no dropouts" (email 2015-4-19).
Selective reporting (reporting bias)	High risk	ICU stay and Hospital stay were not reported since they were not significant
Other bias	Low risk	"All our studies are funded by our university: Tabriz University of Medical Sciences, Tabriz, Iran" (email 2015-10-1)

Sarzaeem 2014

Methods	Randomised placebo-controlled secondary prevention trial.
Participants	Iran, CABG patients, 118 M / 52 F, mean 59 yr (SD 10 yr) ; 85 vit C / 85 placebo **Inclusion:** Patients with coronary artery disease (in angiography) who were candidates for coronary artery bypass **Exclusion:** >80 yr, AF before surgery; valvular heart disease, arrhythmia, or cardiac conduction block of any degree; pacemaker, chronic lung, liver, or kidney disease; other heart surgeries along with CABG, history of antiarrhythmic drug consumption, sick sinus syndrome; symptoms or history of urinary calculi, vitamin C consumption during the last 3 months
Interventions	**Vit C before the operation:** **Dose:** 2 g **Method:** iv **Timing:** "12 h before the procedure" **Vit C after operation:** **Dose:** 1 g/d **Method:** iv **Duration:** 5 d. **Placebo:** "patients in the control group received placebo (normal saline intravenously)" (abstract)
Outcomes	POAF (Analysis 1.1), Length of hospital stay (Analysis 2.1), Length of ICU stay (Analysis 3.1).
Notes	The report was published in Farsi (Persian) with an abstract in English No reply to our emails. We arranged translation of the report to English. In table, the results were reported to one digit. The text section reports that the difference between groups in length of hospital stay was 1.53 d and in length of ICU stay was 0.49 days. Therefore we adjusted the vitamin C hospital stay to 6.67 d and ICU stay to 2.51 d, keeping the placebo group values as in the table

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"using a table of random numbers are divided into intervention and control groups to receive placebo or vitamin C" (abstract)
Allocation concealment (selection bias)	Low risk	Double-blind implies allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"this double-blind, parallel clinical trial" (Abstract), "The present study was a double-blind parallel group clinical trial, because neither the

Sarzaeem 2014 (*Continued*)

		patients nor the health care workers were aware of the medications in the infusions" (Methods)-
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

van Wagoner 2003

Methods	Randomised placebo-controlled secondary prevention trial.
Participants	USA, CABG patients 400 randomized, 338 analyzed; age 63 yr; 172 vit C / 166 placebo **Inclusion:** Patients undergoing CABG. **Exclusion:** Patients with a history of AF, combined surgery (valve+CABG)
Interventions	**Vit C before the operation:** **Dose:** 2 g **Method:** po **Timing:** "night before surgery" **Vit C after operation:** **Dose:** 1 g/d **Method:** po **Duration:** 5 d. "the same dosing strategy" as in Carnes 2001) **Placebo**
Outcomes	POAF
Notes	Reported very briefly within a review in Van Wagoner 2008. Additional information was received by email from David van Wagoner on 2015-9-2 and 2015-9-25, see below No full report was available. We contacted Dr. van Wagoner, and it is possible we will get the results, but we did not get them in time for the deadline of this submission. We will add them later, if we get them

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Low risk	"randomized, blinded trial" (p 308) "there was a randomization table that had been created" (email 2015-9-25). Randomization was done in pairs with SAS procedure PLAN (email 2015-9-29)
Allocation concealment (selection bias)	Low risk	"double blind" implies allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind ... Our investigational pharmacy did the blinding, so all patients and staff were blinded to the treatment." (email 2015-9-2)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind ... Our investigational pharmacy did the blinding, so all patients and staff were blinded to the treatment." (email 2015-9-2)
Incomplete outcome data (attrition bias) All outcomes	Low risk	" Of the 400 total patients enrolled, 54 were dropped from analysis as they either did not go to surgery, surgery was delayed, they had a combined procedure (valve + CABG), or it was found that they had a history of AF after enrollment." (email 2015-9-28)
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Albiez 2003	A trial on vitamin C for cardiac patients, but no data on POAF
Basili 2010	A trial on vitamin C for cardiac patients, but no data on POAF
Carnes 2001	Vitamin C administered to a group of cardiac surgery patients, but comparison to historical controls
Dingchao 1994	No description whether the trial was randomised. A trial on vitamin C for cardiac patients, but no data on POAF
Ibrahim 2010	Not a parallel comparison study. 142 patients were administered vitamin C before surgery and they were compared with 1589 historical controls

(*Continued*)

Oktar 2001	A trial on vitamin C for cardiac patients, but no data on POAF
Wang 2014	A trial on vitamin C for cardiac patients, but no data on POAF

DATA AND ANALYSES

Comparison 1. Occurrence of AF in high risk patients

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Effect of vitamin C	13	1641	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.56, 0.75]
1.1 AF after cardiac surgery (POAF)	12	1597	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.57, 0.77]
1.2 AF recurrence after a successful cardioversion	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.02, 0.92]
2 POAF: Vitamin C in the US vs non-US studies	12	1597	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.57, 0.77]
2.1 non-US trials	8	1012	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.46, 0.67]
2.2 US trials	4	585	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.72, 1.21]
3 POAF: Vitamin C in the Iran vs non-Iran studies	12	1597	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.57, 0.77]
3.1 Iran trials	5	780	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.39, 0.62]
3.2 non-Iran trials	7	817	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.69, 1.01]
4 POAF: iv vs. oral vitamin C	8	1012	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.46, 0.67]
4.1 Oral vit C	4	360	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.15, 0.48]
4.2 Intravenous vit C	4	652	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.53, 0.78]
5 POAF: Vitamin C effects in subgroups	12	1597	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.57, 0.77]
5.1 non-US oral vit C	4	360	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.15, 0.48]
5.2 non-US intravenous vit C	4	652	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.53, 0.78]
5.3 US trials	4	585	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.72, 1.21]

Comparison 2. Length of hospital stay

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Effect of vitamin C (in %)	9	1399	Mean Difference (IV, Fixed, 95% CI)	-11.39 [-15.19, -7.59]
2 Effect of vitamin C (in days)	9	1399	Mean Difference (IV, Fixed, 95% CI)	-0.73 [-1.00, -0.45]
3 Effect of vitamin C in subgroups (in %)	9	1399	Mean Difference (IV, Fixed, 95% CI)	-11.39 [-15.19, -7.59]
3.1 Intravenous vit C	4	652	Mean Difference (IV, Fixed, 95% CI)	-17.76 [-23.43, -12.09]
3.2 Oral vit C	5	747	Mean Difference (IV, Fixed, 95% CI)	-6.22 [-11.33, -1.11]

Comparison 3. Length of ICU stay

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Effect of vitamin C (in %)	8	1061	Mean Difference (IV, Fixed, 95% CI)	-8.85 [-13.68, -4.03]

Comparison 4. Length of mechanical ventilation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Effect of vitamin C (in %)	4	594	Mean Difference (IV, Fixed, 95% CI)	-14.95 [-22.89, -5.00]

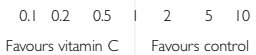
Analysis 1.1. Comparison 1 Occurrence of AF in high risk patients, Outcome 1 Effect of vitamin C.

Review: Vitamin C for treating atrial fibrillation

Comparison: 1 Occurrence of AF in high risk patients

Outcome: 1 Effect of vitamin C

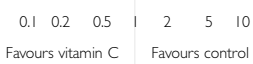
Study or subgroup	Vitamin C n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 AF after cardiac surgery (POAF)					
Eslami 2007	2/50	13/50		4.3 %	0.15 [0.04, 0.65]
Rebrova 2012	1/20	4/20		1.3 %	0.25 [0.03, 2.05]
Dehghani 2014	4/50	16/50		5.3 %	0.25 [0.09, 0.70]
Samadikhah 2014	6/60	15/60		5.0 %	0.40 [0.17, 0.96]
Healy 2010	5/19	7/11		3.0 %	0.41 [0.17, 0.99]
Sarzaeem 2014	11/85	25/85		8.4 %	0.44 [0.23, 0.84]
Sadeghpour 2015	40/113	99/177		25.8 %	0.63 [0.48, 0.84]
Colby 2011	4/13	5/11		1.8 %	0.68 [0.24, 1.92]
Papoulidis 2011	38/85	52/85		17.4 %	0.73 [0.55, 0.98]
Polymeropoulos 2015	4/11	5/11		1.7 %	0.80 [0.29, 2.21]



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Vitamin C n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bjordahl 2012	27/89	29/96		9.3 %	1.00 [0.65, 1.56]
van Wagoner 2003	44/177	41/169		14.0 %	1.02 [0.71, 1.48]
Subtotal (95% CI)	**772**	**825**		**97.3 %**	**0.66 [0.57, 0.77]**
Total events: 186 (Vitamin C), 311 (Control)					
Heterogeneity: Chi^2 = 21.71, df = 11 (P = 0.03); I^2 =49%					
Test for overall effect: Z = 5.40 (P < 0.00001)					
2 AF recurrence after a successful cardioversion					
Korantzopoulos 2005	1/22	8/22		2.7 %	0.13 [0.02, 0.92]
Subtotal (95% CI)	**22**	**22**		**2.7 %**	**0.13 [0.02, 0.92]**
Total events: 1 (Vitamin C), 8 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.04 (P = 0.041)					
Total (95% CI)	**794**	**847**		**100.0 %**	**0.65 [0.56, 0.75]**
Total events: 187 (Vitamin C), 319 (Control)					
Heterogeneity: Chi^2 = 24.75, df = 12 (P = 0.02); I^2 =52%					
Test for overall effect: Z = 5.71 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 2.68, df = 1 (P = 0.10), I^2 =63%					

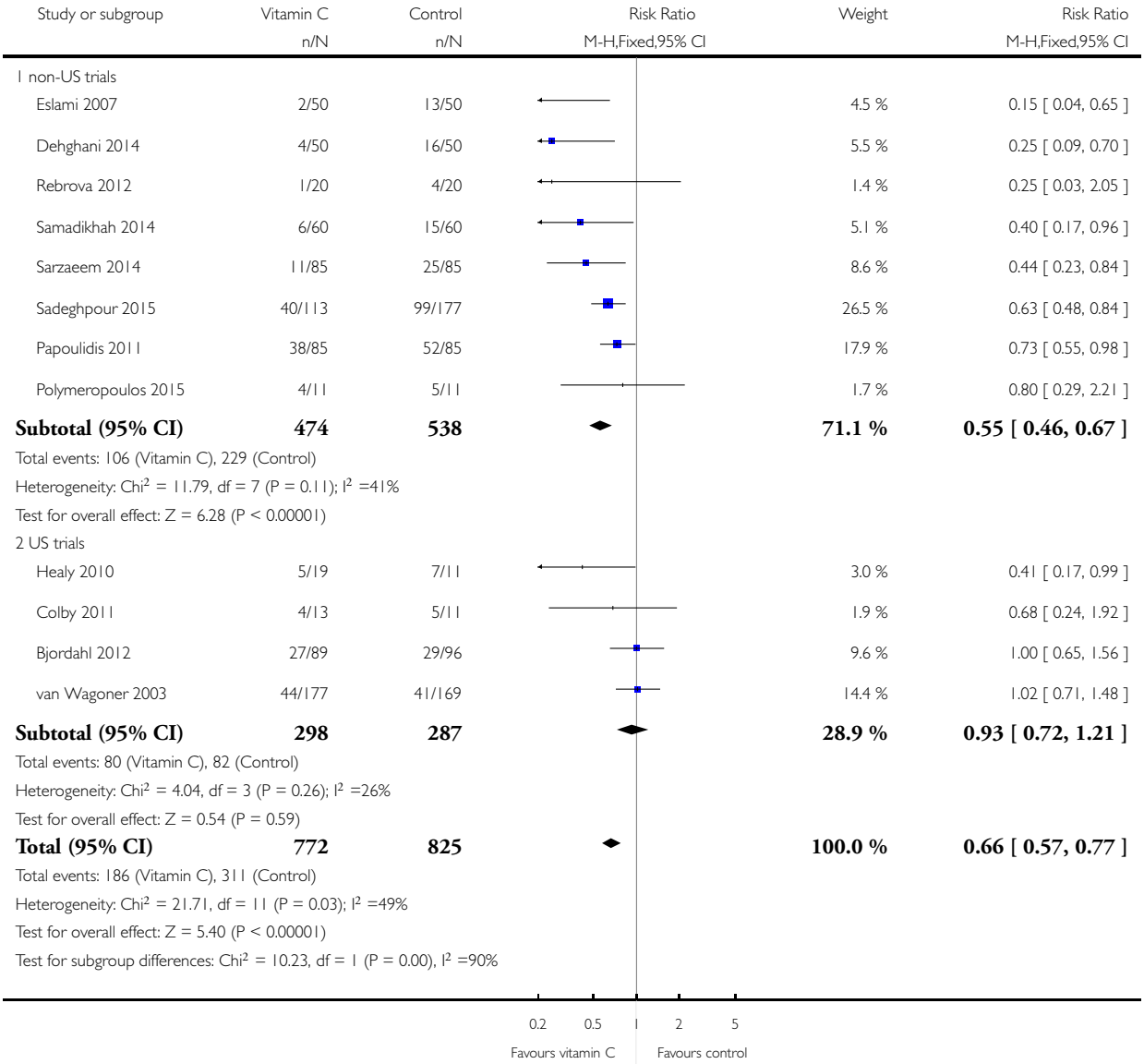


Analysis 1.2. Comparison 1 Occurrence of AF in high risk patients, Outcome 2 POAF: Vitamin C in the US vs non-US studies.

Review: Vitamin C for treating atrial fibrillation

Comparison: 1 Occurrence of AF in high risk patients

Outcome: 2 POAF: Vitamin C in the US vs non-US studies

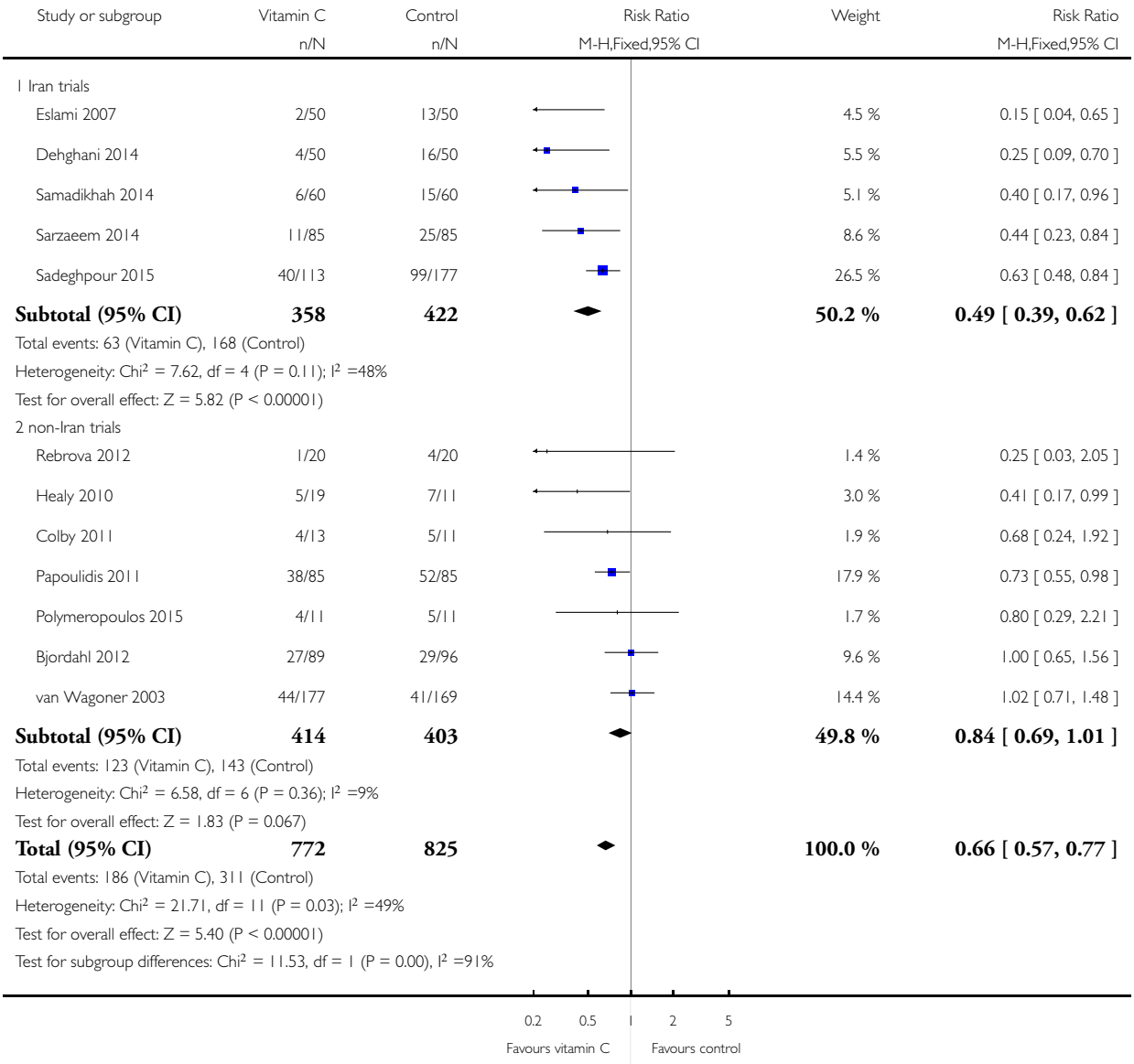


Analysis 1.3. Comparison 1 Occurrence of AF in high risk patients, Outcome 3 POAF: Vitamin C in the Iran vs non-Iran studies.

Review: Vitamin C for treating atrial fibrillation

Comparison: 1 Occurrence of AF in high risk patients

Outcome: 3 POAF: Vitamin C in the Iran vs non-Iran studies

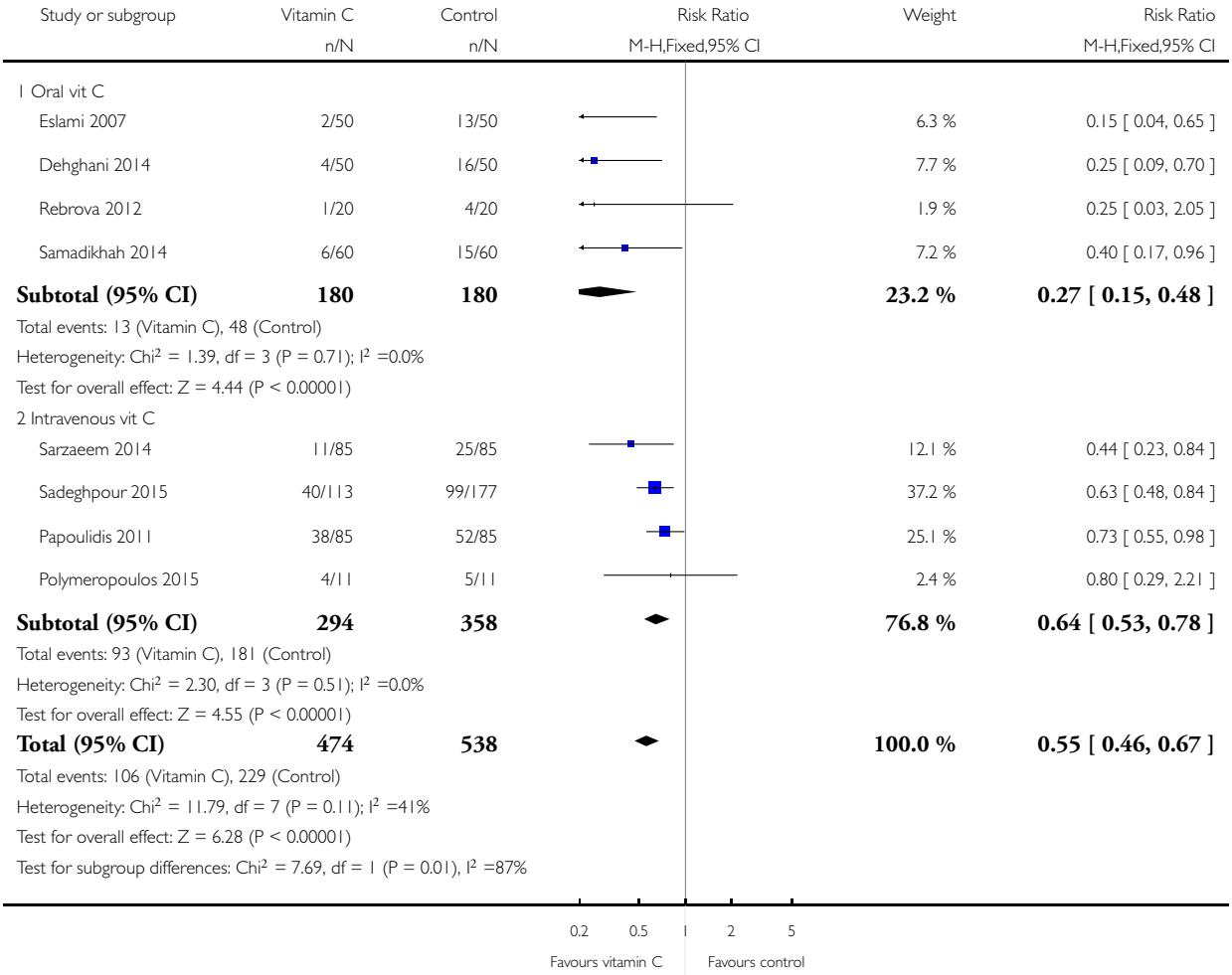


Analysis 1.4. Comparison 1 Occurrence of AF in high risk patients, Outcome 4 POAF: iv vs. oral vitamin C.

Review: Vitamin C for treating atrial fibrillation

Comparison: 1 Occurrence of AF in high risk patients

Outcome: 4 POAF: iv vs. oral vitamin C

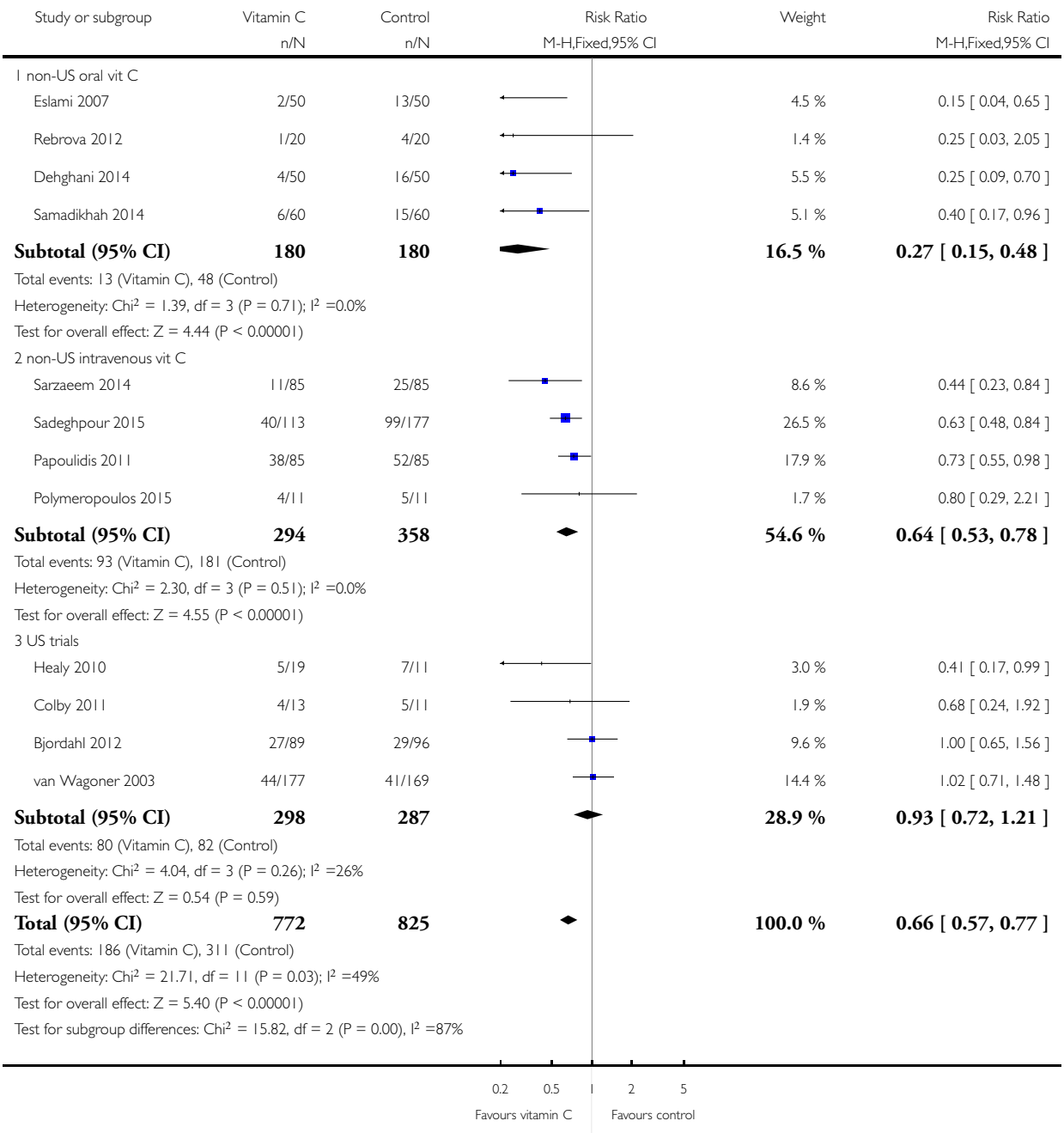


Analysis 1.5. Comparison 1 Occurrence of AF in high risk patients, Outcome 5 POAF: Vitamin C effects in subgroups.

Review: Vitamin C for treating atrial fibrillation

Comparison: 1 Occurrence of AF in high risk patients

Outcome: 5 POAF: Vitamin C effects in subgroups



Analysis 2.1. Comparison 2 Length of hospital stay, Outcome 1 Effect of vitamin C (in %).

Review: Vitamin C for treating atrial fibrillation

Comparison: 2 Length of hospital stay

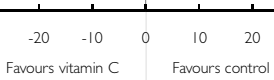
Outcome: 1 Effect of vitamin C (in %)

Study or subgroup	Vitamin C N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Papoulidis 2011	85	80.61 (61)	85	100 (61)		4.3 %	-19.39 [-37.73, -1.05]
Sarzaeem 2014	85	81.34 (18)	85	100 (28)		28.8 %	-18.66 [-25.74, -11.58]
Sadeghpour 2015	113	84.75 (49)	177	100 (49)		10.8 %	-15.25 [-26.81, -3.69]
Polymeropoulos 2015	11	88.53 (42)	11	100 (52)		0.9 %	-11.47 [-50.97, 28.03]
Bjordahl 2012	89	88.89 (34)	96	100 (61)		7.3 %	-11.11 [-25.21, 2.99]
Eslami 2007	50	92.37 (46)	50	100 (49)		4.2 %	-7.63 [-26.26, 11.00]
Dehghani 2014	50	92.68 (10)	50	100 (23)		29.9 %	-7.32 [-14.27, -0.37]
van Wagoner 2003	172	98.63 (48)	166	100 (48)		13.8 %	-1.37 [-11.61, 8.87]
Colby 2011	13	143 (172)	11	100 (48)		0.2 %	43.00 [-54.71, 140.71]
Total (95% CI)	**668**		**731**			**100.0 %**	**-11.39 [-15.19, -7.59]**

Heterogeneity: Chi^2 = 11.56, df = 8 (P = 0.17); I^2 =31%

Test for overall effect: Z = 5.88 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2 Length of hospital stay, Outcome 2 Effect of vitamin C (in days).

Review: Vitamin C for treating atrial fibrillation

Comparison: 2 Length of hospital stay

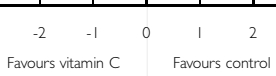
Outcome: 2 Effect of vitamin C (in days)

Study or subgroup	Vitamin C N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Papoulidis 2011	85	7.9 (6)	85	9.8 (6)		2.3 %	-1.90 [-3.70, -0.10]
Sadeghpour 2015	113	10.17 (5.9)	177	12 (5.9)		3.9 %	-1.83 [-3.22, -0.44]
Sarzaeem 2014	85	6.67 (1.5)	85	8.2 (2.3)		22.0 %	-1.53 [-2.11, -0.95]
Polymeropoulos 2015	11	11.27 (5.31)	11	12.73 (6.6)		0.3 %	-1.46 [-6.47, 3.55]
Bjordahl 2012	89	10.4 (4)	96	11.7 (7.1)		2.8 %	-1.30 [-2.95, 0.35]
Eslami 2007	50	6.54 (3.24)	50	7.08 (3.45)		4.3 %	-0.54 [-1.85, 0.77]
Dehghani 2014	50	5.32 (0.59)	50	5.74 (1.3)		47.8 %	-0.42 [-0.82, -0.02]
van Wagoner 2003	172	6.529 (3.15)	166	6.62 (3.15)		16.6 %	-0.09 [-0.76, 0.58]
Colby 2011	13	14.6 (17.6)	11	10.2 (4.9)		0.1 %	4.40 [-5.60, 14.40]
Total (95% CI)	**668**		**731**			**100.0 %**	**-0.73 [-1.00, -0.45]**

Heterogeneity: Chi^2 = 18.70, df = 8 (P = 0.02); I^2 =57%

Test for overall effect: Z = 5.21 (P < 0.00001)

Test for subgroup differences: Not applicable



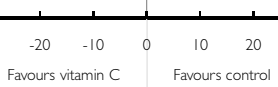
Analysis 2.3. Comparison 2 Length of hospital stay, Outcome 3 Effect of vitamin C in subgroups (in %).

Review: Vitamin C for treating atrial fibrillation

Comparison: 2 Length of hospital stay

Outcome: 3 Effect of vitamin C in subgroups (in %)

Study or subgroup	Vitamin C N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Intravenous vit C							
Papoulidis 2011	85	80.61 (61)	85	100 (61)		4.3 %	-19.39 [-37.73, -1.05]
Sarzaeem 2014	85	81.34 (18)	85	100 (28)		28.8 %	-18.66 [-25.74, -11.58]
Sadeghpour 2015	113	84.75 (49)	177	100 (49)		10.8 %	-15.25 [-26.81, -3.69]
Polymeropoulos 2015	11	88.53 (42)	11	100 (52)		0.9 %	-11.47 [-50.97, 28.03]
Subtotal (95% CI)	**294**		**358**			**44.8 %**	**-17.76 [-23.43, -12.09]**
Heterogeneity: Chi² = 0.37, df = 3 (P = 0.95); I² =0.0%							
Test for overall effect: Z = 6.14 (P < 0.00001)							
2 Oral vit C							
Bjordahl 2012	89	88.89 (34)	96	100 (61)		7.3 %	-11.11 [-25.21, 2.99]
Eslami 2007	50	92.37 (46)	50	100 (49)		4.2 %	-7.63 [-26.26, 11.00]
Dehghani 2014	50	92.68 (10)	50	100 (23)		29.9 %	-7.32 [-14.27, -0.37]
van Wagoner 2003	172	98.63 (48)	166	100 (48)		13.8 %	-1.37 [-11.61, 8.87]
Colby 2011	13	143 (172)	11	100 (48)		0.2 %	43.00 [-54.71, 140.71]
Subtotal (95% CI)	**374**		**373**			**55.2 %**	**-6.22 [-11.33, -1.11]**
Heterogeneity: Chi² = 2.42, df = 4 (P = 0.66); I² =0.0%							
Test for overall effect: Z = 2.38 (P = 0.017)							
Total (95% CI)	**668**		**731**			**100.0 %**	**-11.39 [-15.19, -7.59]**
Heterogeneity: Chi² = 11.56, df = 8 (P = 0.17); I² =31%							
Test for overall effect: Z = 5.88 (P < 0.00001)							
Test for subgroup differences: Chi² = 8.77, df = 1 (P = 0.00), I² =89%							



Analysis 3.1. Comparison 3 Length of ICU stay, Outcome 1 Effect of vitamin C (in %).

Review: Vitamin C for treating atrial fibrillation

Comparison: 3 Length of ICU stay

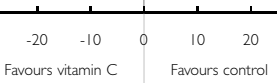
Outcome: 1 Effect of vitamin C (in %)

Study or subgroup	Vitamin C N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Papoulidis 2011	85	76.19 (79)	85	100 (79)		4.1 %	-23.81 [-47.56, -0.06]
Sarzaeem 2014	85	83.67 (46)	85	100 (53)		10.5 %	-16.33 [-31.25, -1.41]
Dehghani 2014	50	85.24 (15)	50	100 (29)		28.5 %	-14.76 [-23.81, -5.71]
Bjordahl 2012	89	86.05 (51)	96	100 (68)		7.8 %	-13.95 [-31.19, 3.29]
Polymeropoulos 2015	11	87.76 (35.83)	11	100 (40.21)		2.3 %	-12.24 [-44.07, 19.59]
Eslami 2007	50	88.46 (62)	50	100 (57)		4.3 %	-11.54 [-34.88, 11.80]
Sadeghpour 2015	113	99.71 (31)	177	100 (32)		42.5 %	-0.29 [-7.70, 7.12]
Colby 2011	13	217 (511)	11	100 (88)		0.0 %	117.00 [-165.60, 399.60]
Total (95% CI)	**496**		**565**			**100.0 %**	**-8.85 [-13.68, -4.03]**

Heterogeneity: Chi^2 = 10.45, df = 7 (P = 0.16); I^2 =33%

Test for overall effect: Z = 3.59 (P = 0.00033)

Test for subgroup differences: Not applicable

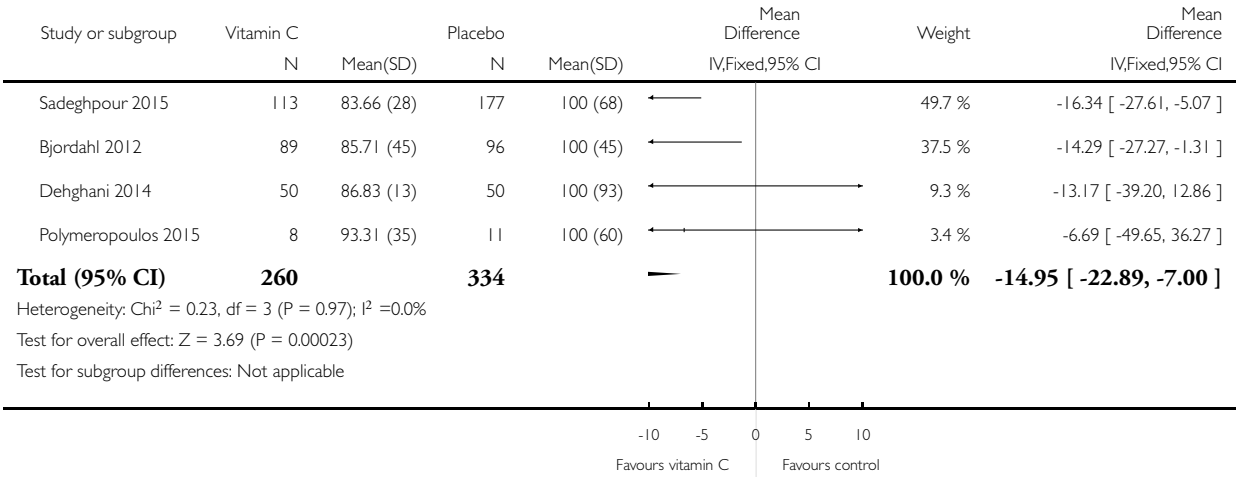


Analysis 4.1. Comparison 4 Length of mechanical ventilation, Outcome 1 Effect of vitamin C (in %).

Review: Vitamin C for treating atrial fibrillation

Comparison: 4 Length of mechanical ventilation

Outcome: 1 Effect of vitamin C (in %)



ADDITIONAL TABLES

Table 1. NNTB in vitamin C and AF trials

Trial	Incidence in the vit C group	Incidence in the control group	Difference in incidence	NNTB
Dehghani 2014	8%	32%	24%	4.2
Eslami 2007	4%	26%	22%	4.5
Korantzopoulos 2005	4.5%	36%	32%	3.1
Papoulidis 2011	45%	61%	16%	6.1
Sadeghpour 2015	35%	56%	21%	4.9
Samadikhah 2014	10%	25%	15%	6.6
Sarzaeem 2014	13%	29%	16%	6.1

NNTB; Number Needed to Treat to Benefit; the number of people who need to be treated so that one of them gets benefit.

APPENDICES

Appendix 1. Searches March 2015

CENTRAL

#1MeSH descriptor: [Ascorbic Acid] this term only
#2ascorb*:ti,ab,kw (Word variations have been searched)
#3(vit* near/6 c):ti,ab,kw (Word variations have been searched)
#4magnorbin:ti,ab,kw (Word variations have been searched)
#5hybrin:ti,ab,kw (Word variations have been searched)
#6#1 or #2 or #3 or #4 or #5
#7MeSH descriptor: [Atrial Fibrillation] this term only
#8atrial fibrillation*:ti,ab,kw (Word variations have been searched)
#9auricular fibrillation*:ti,ab,kw (Word variations have been searched)
#10atrium fibrillation*:ti,ab,kw (Word variations have been searched)
#11af:ti,ab,kw (Word variations have been searched)
#12a-fib:ti,ab,kw (Word variations have been searched)
#13#7 or #8 or #9 or #10 or #11 or #12
#14#6 and #13

MEDLINE OVID

1 Ascorbic Acid/
2 ascorb*.tw.
3 (vit* adj6 c).tw.
4 magnorbin.tw.
5 hybrin.tw.
6 or/1-5
7 Atrial Fibrillation/
8 atrial fibrillation*.tw.
9 auricular fibrillation*.tw.
10 atrium fibrillation*.tw.
11 af.tw.
12 a-fib.tw.
13 or/7-12
14 6 and 13

EMBASE OVID

1 Ascorbic Acid/
2 ascorb*.tw.
3 (vit* adj6 c).tw.
4 magnorbin.tw.
5 hybrin.tw.
6 or/1-5
7 Atrial Fibrillation/
8 atrial fibrillation*.tw.
9 auricular fibrillation*.tw.
10 atrium fibrillation*.tw.
11 af.tw.
12 a-fib.tw.

13 or/7-12
14 6 and 13

CONTRIBUTIONS OF AUTHORS

HH wrote the draft for the protocol. TS participated in the revision of the protocol draft. HH and TS independently screened the titles and abstracts to decide whether a study should be included. HH and TS independently read the reports for studies to be included and assessed the methods and extracted the findings. HH input the date to the RevMan program and TS checked the data. HH wrote a draft for the review and TS participated in the revision of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- New Source of support, Other.

External sources

- No external funding, Finland.
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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the Protocol, we wrote in the section Types of studies: "In treatment trials reporting on the duration of hospitalization and the incidence of HF associated with AF, we will restrict these to placebo controlled trials, since it is possible that the lack of placebo might bias observations on such outcomes." We did not find any treatment trials and we removed this plan. We also re-considered the possibility of placebo effect influencing the length of mechanical ventilation or ICU stay or hospital stay, and it seemed to us highly unlikely that the absence of explicit placebo might influence these outcomes. Nevertheless, we carried out sensitivity analysis and excluded trials that did not use placebo from our analysis of hospital stay, which we consider the most important of these three outcomes.

In the Protocol, we wrote in the section Secondary outcomes: "If there are data on the effect of vitamin C on quality of life and economic costs, they will be described." In this review we modified this plan to cover the length of hospital stay, the length of ICU stay and the length of mechanical ventilation as operational outcomes reflecting quality of life and economic costs, since we found that these three outcomes were reported in several studies so that a meaningful meta-analysis was feasible.

In our procotol, we planned that if there are suitable data available, we were

interested in the potential role vitamin C status as a subgroup variable. None of the included studies reported vitamin C status of the patients. After seeing the included studies we observed that there was substantial divergence in the effects of vitamin C in the US studies and in the Iran studies and we decided to carry out a post hoc subgroup analysis by the countries so that we contrasted US and non-US studies, and Iran and non-Iran studies. This country-based subgroup analysis is not unnambiguously inconsistent with the concept of dietary vitamin C intake influencing the effects of vitamin C supplementation, since it is possible that the average intake is lower in Iran than in the USA.