Vitamin K for improved anticoagulation control in patients receiving warfarin

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What's new

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History

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Abstract

Background

Effective use of warfarin involves keeping the international normalised ratio (INR) within a relatively narrow therapeutic range. However, patients respond widely to their dose of warfarin. Overcoagulation can lead to an increased risk of excessive bleeding, while undercoagulation can lead to increased clot formation. There is some evidence that patients with a variable response to warfarin may benefit from a concomitant low dose of vitamin K.

Objectives

To assess the effects of concomitant supplementation of low-dose oral vitamin K for anticoagulation control in patients being initiated on or taking a maintenance dose of warfarin.

Search methods

To identify previous reviews, we searched the Database of Abstracts of Reviews of Effects (DARE via *The Cochrane Library*, Wiley) (Issue 2, 2011). To identify primary studies, we searched the Cochrane Central Register of Controlled Trials (CENTRAL via *The Cochrane Library*, Wiley) (Issue 2, 2014), Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations database and Ovid MEDLINE (R) (OvidSP) (1946 to 25 February 2014), Embase (OvidSP) (1974 to week 8 of 2014), Science Citation Index Expanded™ & Conference Proceedings Citation Index - Science (Web of Science™) (1945 to 27 February 2014), and the NHS Economics Evaluations Database (NHS EED) (via *The Cochrane Library*, Wiley) (Issue 2, 2014). We did not apply any language or date restrictions. We used additional methods to identify grey literature and ongoing studies.

Selection criteria

Randomised controlled trials comparing the addition of vitamin K versus placebo in patients initiating warfarin or already taking warfarin.

Data collection and analysis

Two review authors independently selected and extracted data from included studies. When disagreement arose, a third author helped reached a consensus. We also assessed risk of bias.

Main results

We identified two studies with a total of 100 participants for inclusion in the review. We found the overall risk of bias to be unclear in a number of domains. Neither study reported the time taken to the first INR in range. Only one study (70 participants) reported the mean time in therapeutic range as a percentage. This study found that in the group of participants deemed to have poor INR control, the addition of 150 micrograms (mcg) oral vitamin K significantly improved anticoagulation control in those with unexplained instability of response to warfarin. The second study (30 participants) reported the effect of 175 mcg oral vitamin K versus placebo on participants with high variability in their INR levels. The study concluded that vitamin K supplementation did not significantly improve the stability of anticoagulation for participants on chronic anticoagulation therapy. However, the study was only available in abstract form, and communication with the lead author confirmed that there were no further publications. Therefore, we interpreted this conclusion with caution. Neither study reported any thromboembolic events, haemorrhage, or death from the addition of vitamin K supplementation.

Authors' conclusions

Two included studies in this review compared whether the addition of a low dose (150 to 175 mcg) of vitamin K given to participants with a high-variability response to warfarin improved their INR control. One study demonstrated a significant improvement, while another smaller study (published in abstract only) suggested no overall benefit. Currently, there are insufficient data to suggest an overall benefit. Larger, higher quality trials are needed to examine if low-dose vitamin K improves INR control in those starting or already taking warfarin.

Plain language summary

The addition of vitamin K to improve anticoagulation stability for patients starting or already on warfarin

People with irregularity in heart activity, mechanical heart valves, and clotting disorders are at increased risk of developing blood clots, which could lead to stroke or death. Taking warfarin significantly reduces this risk. However, taking too much warfarin can lead to excessive bleeding, while taking too little reduces its benefit. To monitor this, patients taking warfarin must have regular blood tests to check if their dose of warfarin is stable enough to find the correct balance. There is some evidence that adding a small dose of vitamin K to the warfarin improves this balance. In this review, our primary outcomes were to assess if the addition of low-dose vitamin K to warfarin had an effect on the time taken to the first INR in range; the mean within the therapeutic range; or any adverse events, such as thromboembolic events, haemorrhage, or mortality. We found two studies that met our inclusion criteria. Neither study reported the time taken to the first INR in range. One study was only available in an abbreviated format, so we were unable to interpret the results fully. Nonetheless, it was suggested that the addition of vitamin K had no benefit. A second six-month study gave a small dose of vitamin K (150 mcg daily) or placebo to participants taking warfarin with existing poor INR control. This study reported the mean time in therapeutic range as a percentage and found that in the group of participants deemed to have poor INR control, the addition of 150 mcg oral vitamin K significantly improved their anticoagulation control. However, the study was relatively small. Neither study reported any adverse events, such as thromboembolism, haemorrhage, or death. We conclude that further larger, higher quality studies are needed to conclude whether adding vitamin K to warfarin for patients starting or already on warfarin improves their anticoagulation control.

Background

Description of the condition

A substantial number of people require oral anticoagulants: In the United Kingdom (UK), for example, 1.4% of the population require long-term treatment with anticoagulants (NICE 2010). There has been a substantial increase in the use of oral anticoagulants, particularly in the ageing population (van Walraven 2009). The numbers are going to continue to increase by about 10% each year, primarily driven by their use in people with atrial fibrillation (AF) (DTB 2009). Other reasons for the increase include improvements in clinical outcomes (Manotti 2001) and improvements in anticoagulant safety (Ansell 2001).

There are numerous other medical conditions apart from AF that lead to thromboembolic events, including deep vein thrombosis (DVT), cardiovascular causes like mechanical heart valve replacement, cardioversion, cardiomyopathy, and antiphospholipid syndrome (Baglin 2006). Oral anticoagulation therapy with vitamin K antagonists (VKAs) reduces these events (Connolly 1991; Ezekowitz 1992; Go 2003). The main oral VKA used in the UK is warfarin (McIlroy 2009). Vitamin K is a cofactor needed for the liver synthesis of factors II, VII, IX, and X, all of which are involved in the coagulation cascade. VKAs inhibit the regeneration of vitamin K hydroquinone from vitamin K epoxide by inhibiting the reductase enzymes in the vitamin K cycle (Choonara 1988). The duration of the use of warfarin depends on the medical conditions; for an isolated calf vein thrombosis, warfarin is indicated for six weeks, whereas for mechanical heart valve, it is indicated for lifelong use (Baglin 2006).

Whilst warfarin prevents thromboembolic events, it can also cause adverse effects like major haemorrhage, particularly if too

much warfarin is being taken and over-anticoagulation occurs (Wan 2008). Similarly, when not enough warfarin is administered, under-anticoagulation may lead to thrombosis, hence, worsening the medical condition the clinician is trying to treat (Wan 2008). The Medicines and Healthcare Products Regulatory Agency (MHRA) received 2233 adverse reaction reports associated with warfarin use between June 1963 and June 2008. The majority of these adverse reactions reported were as a result of over-anticoagulation and bleeding, and the majority of the fatal cases reported were again associated with haemorrhage (208 of the 297 were fatal reports) (MHRA 2009). This was supported by the Adverse Effect Event Monitoring system in the United States (US). From 1993 to 2006, warfarin caused 9766 bleeding cases, including 8415 (86%) cases that led to serious complications including death, hospitalisation, or required intervention. It also showed the reporting of 635 cases as under-anticoagulation with warfarin and 511 cases having problems with coagulopathy (Wysowski 2007).

Therefore, it is important to monitor warfarin levels regularly to prevent under- or over-anticoagulation. Current models of oral anticoagulation management within the UK include the traditional hospital outpatient model and various forms of community-based models, all requiring patient attendance at a clinic (Fitzmaurice 2002). In other countries, such as Canada, a primary care physician manages oral anticoagulation (Sunderji 2004).

The international normalised ratio (INR) is used to monitor the therapeutic level of warfarin. This level varies according to the condition being treated. For example, an INR of 2.0 to 3.0 is adequate for the prevention of thromboembolic events in AF, and an INR of 3.0 to 4.0 is adequate for mitral valve replacement. So, for the former example, if INR is less than two, then under-coagulation results, and if INR is greater than three, over-anticoagulation occurs. Maintaining individuals within the narrow therapeutic ranges for INR can prove challenging in routine clinical practice. The percentage of time of INR in therapeutic range could be as low as 29% (Wan 2008). A study of longitudinal INR levels among a cohort of participants with AF showed only 33% of participants' INR was in therapeutic range (Rosenman 2009).

Description of the intervention

At the initiation stage of warfarin treatment, it is important to select the correct warfarin dose and to maintain individuals within their therapeutic range (Heneghan 2010). Attempts to stabilise patients on warfarin include checking daily INR levels after the introduction of the initial dose until INR results are in the therapeutic INR range. If one of the known medications that interact with warfarin is initiated or an intercurrent illness coexists, there will be an increase in the frequency of INR monitoring, and warfarin doses will be readjusted and monitored again (Ford 2008). Another attempt at stabilisation is to self-test the INR levels and to self-monitor the warfarin dose with the help of computer programs by patients themselves (Heneghan 2006).

Despite these attempts, however, it has been shown that up to half of all patients who receive warfarin to control coagulation fail to stabilise within their target range, particularly in the first five days of treatment (Heneghan 2006). The pharmacokinetics of warfarin can be affected by various dietary substances that contain vitamin K and also medications which then result in under- or over-anticoagulation (Holbrook 2005). Interactions with certain medications, such as macrolides, antibiotics, nonsteroidal anti-inflammatory drugs, lipid-lowering agents, and amiodarone; and certain foods that are rich in vitamin K, such as brussel sprouts and broccoli, can interfere with the warfarin blood levels, and over- or under-anticoagulation subsequently occurs (Holbrook 2005).

There is little storage of vitamin K in the body; therefore, the production of vitamin K-dependent clotting factors and proteins are highly dependent on dietary vitamin K. A brief period of reduced intake of vitamin K can cause warfarin sensitivity, and an increased intake of vitamin K-containing foods can reduce anticoagulation; both of these effects can last afterwards for several days (Franco 2004). Patients with unstable control of anticoagulation have a consistently and significantly lower intake of vitamin K than their stable counterparts matched for age, sex, and indication for warfarin (Sconce 2005). Patients who were allocated to an 80% decrease of vitamin K intake increased their INR by almost 30% seven days after the intervention. Similarly, it was estimated by the dietary records that each increase in 100 micrograms (mcg) of vitamin K intake reduced the INR by 0.2 (Rohde 2007).

In order to have a relatively stable control of warfarin in practice, clinicians often advise patients to eat a relatively similar amount of vitamin K-containing foods on a regular basis rather than eating a large serving occasionally. There are sufficient data to suggest that a constant dietary intake of vitamin K that meets current dietary recommendations of 65 to 80 micrograms/day is the most acceptable dietary advice that is given to patients on warfarin therapy (Booth 1999).

This approach is supported by randomised controlled trial evidence, which shows that 74% of participants mainly with mechanical heart valves or AF on dietary vitamin K-guided management strategy were on target for the prespecified INR at 90 days compared with 58% of participants managed conventionally (de Assis 2009). However, to have a stable intake of vitamin K-containing foods in practice is often difficult if not impossible to achieve.

How the intervention might work

Having a regular oral vitamin K supplement taken together with a maintenance dose of warfarin improves the stability of INR (Rombouts 2007; Sconce 2007). In one randomised controlled trial, vitamin K supplementation resulted in a significant decrease in the standard deviation of INR compared with placebo, as well as a significantly greater increase in percentage time within target INR range in those patients with unstable INR despite being on warfarin for nine months (Sconce 2007).

Another prospective, randomised, placebo-controlled trial showed that the number of participants in therapeutic range for the duration of the trial doubled in the vitamin K supplementation group compared to the placebo group (43% versus 24%) (Rombouts 2007).

The INR should be checked within a few days of vitamin K initiation to allow for titration of the warfarin dose, and in order to maintain the INR in the therapeutic range, it should be monitored closely in the weeks thereafter (Ford 2007). However, as

vitamin K is taken alongside warfarin and the monitoring schedule does not change greatly (and may even reduce the frequency of monitoring), the assumption is that there will be high acceptability of the intervention.

Why it is important to do this review

It is challenging to achieve and maintain the INR within the therapeutic range without concomitant increases in adverse events. Some medical conditions like DVT require the stability of INR to be achieved as quickly as possible and to continue to maintain in the therapeutic range to reduce adverse events, which in turn will reduce concomitant treatments, such as heparin, or hospital admissions, and reduce costs (Heneghan 2010).

Improving INR control is beneficial in stroke prevention, but it has also been shown to be cost-effective. An analysis of a 1000-patient cohort (mean age 70 years, atrial fibrillation at moderate-to-high risk of stroke, lifetime analysis) showed that the total number of primary and recurrent ischemic strokes was 984 with real-world INR control at a cost of USD 84,518 per patient (Sorensen 2009). However, if such patients had INR values that were always within target range, this would drop to 626 with a cost per patient of USD 68,039 (Sorensen 2009).

An economic model analysed the cost of suboptimal oral anticoagulation and showed the following: If 50% of those not receiving warfarin prophylaxis had optimal anticoagulation, 19,380 emboli would be prevented, and 1.1 billion US dollars could be saved. If 50% of those currently receiving warfarin as part of routine medical care had optimal anticoagulation, 9852 emboli would be prevented, and 1.3 billion US dollars could be saved (Caro 2004).

One possible way to achieve effective anticoagulation control is to have concomitant oral vitamin K supplement. The cost of one tablet of 1 mg of vitamin K is £0.34 (BNF 2013), which would need to be taken into account when considering the wider role-out of low-dose vitamin K to all patients on warfarin. However, low-dose vitamin K could represent a relatively low-cost method for improving INR control for patients taking warfarin.

A systematic review is needed to look for evidence that may have substantial implications in clinical and financial terms, as there has not been any review on this subject.

Objectives

To assess the effects of concomitant supplementation of low-dose oral vitamin K for anticoagulation control in patients being initiated on or taking a maintenance dose of warfarin.

Methods

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) of participants on warfarin in primary care or hospital settings taking concomitant oral vitamin K, compared with placebo or no treatment.

Types of participants

Adults who are over 18 years old and are on warfarin irrespective of the indication for treatment (e.g. valve replacement, AF).

Types of interventions

We included two types of intervention in this review.

Intervention 1: Oral vitamin K (of various doses), which has been added to the loading dose of warfarin. These participants were followed for the duration of the intervention, which is the first five days after initiation of warfarin.

Intervention 2: Oral vitamin K (of various doses), which has been added to the maintenance dose of warfarin. This is a lifelong intervention.

These interventions were compared to either control or placebo groups.

Types of outcome measures

Primary outcomes

- Time taken to the first INR in range (intervention one).
- Mean time of therapeutic range (TTRs) (intervention one).
- Mean time in therapeutic range (intervention two).
- Thromboembolic events included stroke, arterial embolism, symptomatic DVT, or pulmonary embolism (both interventions).
- Major haemorrhage (includes (a) fatal bleeding; (b) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, or pericardial bleeding, or intramuscular with compartment syndrome; (c) bleeding causing a fall in haemoglobin level of 20 g/L-^{1} (1.24 mmol-^{1}) or more, or leading to transfusion of two units of packed red blood cells, or a combination of the aforementioned. (both interventions).
- Mortality (both interventions).

Secondary outcomes

- Proportion of supratherapeutic INRs and subtherapeutic INRs (both interventions).
- Minor haemorrhage (all other haemorragic conditions that are not included in the criteria for major haemorrhage as stated in the primary outcome) (both interventions).

- Rescue medication needed (for example, additional dose of vitamin K) (both interventions).
- Cost-effectiveness (both interventions).
- Quality of life (both interventions).

Search methods for identification of studies

Electronic searches

Search strategies were developed through an iterative process combining subject headings and free-text terms for our population and intervention (Appendix 1). Methodological search filters have been used where appropriate to restrict the search to randomised controlled trials; a Cochrane sensitivity-maximising RCT filter (Lefebvre 2011) has been applied in MEDLINE. No date or language restrictions were applied. In March 2011, we searched for previously published reviews on the Database of Abstracts of Reviews of Effects (DARE in *The Cochrane Library*, Wiley) (Issue 2, 2011). We identified primary studies by searching the following bibliographic databases:

- the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, Wiley) (Issue 2, 2014);
- Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE (R) (OvidSP) (1946 to 25 February 2014);
- Embase (OvidSP) (1974 to week 8 of 2014);
- NHS Economics Evaluations Database (NHS EED) (*The Cochrane Library*, Wiley) (Issue 2, 2014); and
- Science Citation Index Expanded™ (SCI™ Expanded) & Conference Proceedings Citation Index - Science (CPCI-S) (Web of Science™) (1945 to 27 February 2014).

The CENTRAL, MEDLINE, Embase, & NHS EED searches were conducted up to 25 February 2014; the SCI™ Expanded and CPCI-S searches were conducted up to 27 February 2014.

Searching other resources

We performed citation searches and reviewed the references of all full-text papers retrieved. We contacted experts in the field where relevant. We identified ongoing trials that were registered with the WHO International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/), Clinicaltrials.gov (clinicaltrials.gov), and the Current Controlled Trials Register (www.controlled-trials.com) up to 25 February 2014. We identified additional grey literature through a search of OpenGrey (www.opengrey.eu/) up to 25th February 2014. We contacted authors of included studies for additional data and information on ongoing and unpublished trials.

Data collection and analysis

Selection of studies

Two authors (KM and DN) independently assessed relevant titles. We initially excluded irrelevant studies based on title alone and excluded further studies after reviewing the title and abstract. We obtained the full texts of articles deemed to be potentially suitable for inclusion and assessed them against inclusion criteria. At each stage, the two authors (KM and DN) resolved all disagreements through discussion with a third author (CH) until they reached a consensus agreement.

Data extraction and management

We collected data on participants, interventions, and outcomes using a specifically designed data extraction form. Two authors (KM and DN) carried out independent dual extraction of data; they resolved differences between their extraction by discussion and, where necessary, in consultation with a third author (CH). In cases where the data were insufficiently reported, we made attempts to contact the relevant authors.

Assessment of risk of bias in included studies

Two review authors (KM and DN) independently assessed risk of bias using The Cochrane Collaboration's tool for assessing risk of bias. The specific aspects assessed included method of randomisation, allocation concealment, blinding of outcome assessors, treatment of incomplete outcome data, selective reporting, and other potential sources of bias. We referred to the *Cochrane Handbook for Systematic Reviews of Interventions* for guidance (Higgins 2011).

Measures of treatment effect

For dichotomous outcomes, we had aimed to compare different regimens using relative risks (RR) and calculate 95% confidence intervals (CIs). For continuous outcomes, we had aimed to use weighted mean difference (WMD) with 95% CIs to summarise the pooled effect. However, there were insufficient data to undertake meta-analysis in this review, but we plan to do this in future updates.

Unit of analysis issues

Where there were studies that used different ways to present the data (for example, with regard to the maintenance of warfarin, the unit of analysis issues may be days in therapeutic range or proportion of participants in therapeutic range), we had planned to contact the authors for clarification by requesting their raw data. We aimed to dichotomise the data so that it was suitable for meta-analysis where possible. We referred to the *Cochrane Handbook for Systematic Reviews of Interventions* for guidance (Higgins 2011). However, there were insufficient data to undertake meta-analysis in this review, but we plan to do this in future updates.

Dealing with missing data

Where any missing data were present, we contacted the study authors to obtain further relevant details. We only analysed

data that were made available to us and had planned to discuss the impact of the missing data in our findings.

Assessment of heterogeneity

We had aimed to use the I² statistic to quantify the level of statistical heterogeneity (Higgins 2011). Where no heterogeneity was present, we had aimed to perform a fixed-effect meta-analysis. Where substantial heterogeneity (I² statistic above 50%) was present, we had planned to consider the potential explanations for this.

Assessment of reporting biases

We had planned to generate a funnel plot to assess publication bias. However, there were insufficient trials to carry this out; we plan to do this in future updates.

Data synthesis

We intended to perform a meta-analysis for a pooled estimate. However, there were insufficient data in this review to carry this out, but we plan to do this in future updates.

Subgroup analysis and investigation of heterogeneity

There were insufficient numbers of included studies to carry out subgroup analysis. However, we plan to do this in future updates.

Sensitivity analysis

There were insufficient numbers of included studies to carry out sensitivity analysis. However, we plan to do this in future updates.

Results

Description of studies

See the 'Characteristics of included studies' tables and the 'Characteristics of excluded studies' tables.

Results of the search

We obtained a total of 4031 references after executing the search strategy. Of these, we deemed 98 papers to be of potential inclusion based on title alone. We excluded 80 of these after reviewing the title and abstract. We examined 18 papers in full. Of these, we excluded 16 for not being relevant. We give our reasons for exclusion in the 'Characteristics of excluded studies ' tables. We carried out citation searching of all excluded papers, although this did not reveal any studies for inclusion. Therefore, we included two studies in this review. Figure 1 is a flow diagram of our search results.

Included studies

We included two randomised controlled trials, involving 100 participants (Dalloul 2010; Sconce 2007). The Sconce 2007 study randomised 70 participants that were already on warfarin but deemed to have poor control to six months of either 150 mcg vitamin K daily supplementation or matched placebo. The Dalloul 2010 study identified 50 patients on warfarin therapy with high variability in their INR levels, but randomised 30 participants to receive supplemented oral vitamin K (175 mcg) daily versus placebo for six months. However, the Dalloul 2010 study was an abstract only, and communication with the corresponding author confirmed that no further data or publications were available (Dalloul 2013). Please see the ' Characteristics of included studies' tables.

Excluded studies

We excluded a total of 15 studies. Two of these studies met our inclusion criteria on all other aspects except they used different alternative vitamin K antagonists to warfarin (Gebuis 2011; Rombouts 2007). The Rombouts 2007 study was a double-blind, randomised, placebo-controlled trial examining the impact of daily vitamin K supplementation on the vitamin K antagonist phenprocoumon. The Gebuis 2011 study was a double-blind, randomised, controlled trial of varying doses of vitamin K and acenocoumarol or phenprocoumon versus acenocoumarol or phenprocoumon alone. However, as our protocol planned to assess specifically the impact of vitamin K supplementation on the vitamin K antagonist warfarin, we excluded the Rombouts 2007 and Gebuis 2011 studies, but noted their results in our discussion. The Ford 2007 study was a prospective, open-label, cross-over study, so we therefore excluded it on the basis that the design did not meet our inclusion criteria. In the de Assis 2009 study, the intervention arm was a dietary vitamin K strategy, in which participants who were overcoagulated were asked to increase their consumption of three vitamin K-rich foods (lettuce, broccoli, and liver) or decrease it if they were undercoagulated. The comparator group was treated according to standard guidelines. We therefore excluded this study as there was no evidence of concomitant vitamin K supplementation when compared with a placebo arm. We excluded the Pengo 1993 study as the aim was to assess the effect of vitamin K versus warfarin discontinuation in overcoagulated participants. We excluded the Shopnick 1998 paper as it tested the effect of vitamin K in overcoagulated participants. The Kim 2001 study examined the effect of a single dose of warfarin versus a single dose of warfarin plus 10 mg of vitamin K in otherwise healthy individuals who would not otherwise require warfarin treatment. This study was a pharmacokinetic study only, and the authors were unanimous in excluding it given the research question specific to this review. The Marongiu 1992, Pedersen 1991, Udall 1968, and Sorano 1993 studies were not randomised controlled trials. Three excluded studies were reviews or commentary pieces (Ford 2008; JFP 2008; Patriquin 2011). The NTR314 2005 citation appeared to be the trial registration of the Rombouts 2007 study. We excluded the Zuchinali 2012 study as it appeared to be an analysis of a trial in which anticoagulation control was adjusted based on prospective dietary vitamin K intake. Please see the 'Characteristics of excluded studies' tables.

Risk of bias in included studies

We assessed bias using Higgins 2011 as our reference. We categorised studies in each area as being high, low, or unclear (see the 'Characteristics of included studies' tables): We presented the results of this assessment in 'Risk of bias' tables, as well as a 'Risk of bias' graph (Figure 2) and a 'Risk of bias' summary (Figure 3).

Allocation (selection bias)

The Sconce 2007 study reported that participants were randomly allocated to two groups. However, the report provided no further details regarding either the method of allocation concealment or the randomisation methods used. The Dalloul 2010 study was available in abstract form only, and we were unable to obtain any further information to assess the method of allocation.

Blinding (performance bias and detection bias)

The Sconce 2007 study reported that the randomly allocated participants were blinded. Participants in each arm of the study were provided with either vitamin K (phytomenadione) (in 20:80 ethanol–deionised water solution) or matching placebo (20:80 ethanol–deionised water solution). Both were dispensed to participants in a 200 mL dark-brown glass bottle (vitamin K is light-sensitive) with a 5 mL volume measuring cup every four weeks. Sconce 2007 also made attempts to ensure blinding of the outcome assessment by ensuring that the pharmacist altering the dose of warfarin was also blinded to the intervention. It was unclear if researchers blinded to the intervention carried out the final assessment of results. Dalloul 2010 was a randomised, double-blind, placebo-controlled study. However, it was published as an abstract only, and we were unable to gain further detailed information after communication with the author (Dalloul 2013).

Incomplete outcome data (attrition bias)

The Sconce 2007 study enrolled 70 participants into the trial. Of these, two participants failed to complete the trial. The study provides details of the outcomes for both participants. (One withdrew because of intervening illness, and the other died before completing the study.) The authors state that neither case was related to the study but opted not to include these data in their final analysis. The Dalloul 2010 study describes 30 participants enrolled into the trial, but from the abstract only, we were unable to identify whether all completed the trial. It was unclear if the Sconce 2007 study used an intention-to-treat principle. The fact that the final analysis did not include two participants suggests not.

Selective reporting (reporting bias)

The Sconce 2007 study outlined primary and secondary outcomes in the methods section. The results of these were presented in the results and discussion section. The Dalloul 2010 study was available in abstract form only.

Other potential sources of bias

The Dalloul 2010 study was available in abstract only, and it is unclear if the full study was not published because the results were equivocal.

Effects of interventions

Effect of vitamin K on improved INR control

Primary outcomes

Time taken to the first INR in range

Neither Sconce 2007 nor the Dalloul 2010 study reported data on the time taken for participants to reach an INR in range.

Mean time of therapeutic range (TTRs)

Neither Sconce 2007 nor the Dalloul 2010 study reported data on the time taken for participants to reach an INR in range.

Mean time in therapeutic range

In the Sconce 2007 study, the authors report the mean time in therapeutic range as a percentage. The 35 participants allocated to the vitamin K group had their INR monitored for six months during the intervention. The mean time in range (expressed as a percentage) was then compared to the value for those same participants in the six months prior to entering the trial. Likewise, a similar methodology was chosen for the 35 participants allocated to the control arm of the trial. The Sconce 2007 study authors reported that anticoagulation control was significantly improved in both cohorts in the six-month study period compared with the previous six months. However, they further report that the vitamin K supplementation resulted in a significantly greater improvement in the stability of anticoagulation. For the vitamin K group, the mean time in range (per cent) was 59 ± 20 before the study and 87 ± 14 after the intervention period (difference 28 ± 20, $P < 0.01$). For the placebo group, the mean time in range (per cent) was 63 ± 18 in the six months before commencement of the study and 78 ± 17 at the end of the study (difference 15 ± 20, $P < 0.01$). The authors report that there were no significant differences in measures of anticoagulation control in the six months prior to the study between the two participant cohorts. The Dalloul 2010 study did not report any data on time in range.

Other markers of improved control

The Sconce 2007 trial reported that the median number of warfarin dosage changes was significantly lower in the group receiving vitamin K supplementation compared to the placebo group (vitamin K group: five changes (range three to seven) six months before the study versus two changes (range zero to five) six months after the study, a difference of -3 (range zero to -5), $P < 0.001$; placebo group: five changes (range three to eight) six months before the study versus three changes (range one to eight) six months after the study, a difference of -2 (range -3 to three), $P < 0.001$). The Dalloul 2010 study

reported no statistically significant difference in the mean number of dose adjustments after treatment with vitamin K (3.9 + 2.8 versus 4.0 + 2.1, P value not given). However, we were unable to carry out any meta-analysis due to the limitations of the available data.

The Sconce 2007 study recruited participants with unstable INR values. A participant was classified unstable if the standard deviation (SD) of INR values was greater than 0.5, and they had had at least three warfarin dose changes in the previous six months. The primary end point was the SD of INR values in the six-month study period compared with the same measurement in the six months immediately prior to the study. They reported that the SD of INR significantly improved in both the vitamin K and placebo groups, but the effect was greater in the vitamin K group (-0.24 ± 0.14 versus -0.11 ± 0.18, no P value was given for this comparison). Sconce 2007 also reported anticoagulation control improved in 33 of 35 participants receiving vitamin K supplementation, whereas in the control arm, only 24 of 33 participants receiving placebo demonstrated some degree of improvement. However, the authors carried out no statistical analysis on these results, but we calculated this to be a significant improvement (odds ratio 6.19, 95% confidence interval 1.22 to 31.26, P = 0.03) (see Analysis 1.1).

Adverse events

The Sconce 2007 trial did not report any thromboembolic events, major or minor haemorrhage, or use of rescue vitamin K in participants enrolled in either arm of the study. They reported that one participant withdrew because of an intervening illness, although they did not cite the illness. However, the authors state that the case was not related to the intervention, and subsequent unblinding of allocation revealed that the participant received placebo. The authors chose not to include this in the final statistical analysis. The Dalloul 2010 study did not provide any data on thromboembolic events, major haemorrhage, minor haemorrhage, or use of rescue vitamin K. This may in part be due to the fact that we were limited to assessing data provided within the abstract only.

Mortality

The Sconce 2007 trial reported that one participant died, although the authors did not cite a reason. However, they stated that the death was unrelated to the study, and subsequent unblinding revealed the participant to have received placebo. The Dalloul 2010 study did not provide any data on mortality.

Secondary outcomes

Proportion of supratherapeutic INRs and subtherapeutic INRs

Neither Sconce 2007 nor the Dalloul 2010 study provided specific data on the proportion of supratherapeutic INRs and subtherapeutic INRs.

Minor haemorrhage (conditions that are excluded from the criteria for major haemorrhage as stated in the primary outcome)

Neither Sconce 2007 nor the Dalloul 2010 study provided specific data on minor haemorrhages.

Rescue medication needed (for example, additional dose of vitamin K)

Neither Sconce 2007 nor the Dalloul 2010 study provided specific data on the need for rescue medication.

Cost-effectiveness

Neither Sconce 2007 nor the Dalloul 2010 study provided specific data on cost-effectiveness.

Quality of life

Neither Sconce 2007 nor the Dalloul 2010 study provided specific data on quality of life.

Discussion

Summary of main results

Only two studies from 2508 citations met the inclusion criteria for our analysis of the effects of concomitant supplementation of low-dose oral vitamin K for anticoagulation control in patients being initiated on or taking a maintenance dose of warfarin (Dalloul 2010; Sconce 2007).

One of these studies (Dalloul 2010) reported no statistically significant difference in the mean number of dose adjustments after concomitant supplementation with vitamin K and concluded that there was no improvement in INR stability with vitamin K supplementation. In contrast, Sconce 2007 reported that anticoagulation control was significantly improved in participants given concomitant vitamin K supplementation. In addition, the stability of anticoagulation, as measured by the mean time in therapeutic range, was significantly higher with supplementary vitamin K (28% versus 15%, P < .01), but there was no overall effect on warfarin dose changes between intervention and placebo arm. Sconce 2007 also reported anticoagulation control improved in 33 of 35 participants receiving vitamin K supplementation, whereas in the control arm, only 24 of 33 participants receiving placebo demonstrated some degree of improvement. However, no statistical analysis was carried out on these results by the authors, but we calculated this to be a significant improvement (odds ratio 6.19, 95% confidence interval 1.22 to 31.26, P = 0.03).

Overall completeness and applicability of evidence

Since we identified only one published study during the process of our review (Sconce 2007), we interpreted our results with caution. We obtained the remaining included study (Dalloul 2010) as an abstract only, and further communication with the corresponding author confirmed that no further publications arose from this (Dalloul 2013). In the Sconce 2007 study, the intervention group received a once-daily concomitant oral supplement of 150 mcg vitamin K, which the authors point out is

approximately twice the recommended daily allowance (RDA). They justify this vitamin K dose by stating that it was deemed necessary to override any variability in dietary vitamin K intake without causing a statistically significant lowering of the INR (Sconce 2007). Furthermore, the Sconce 2007 study reported median dose changes six months before the intervention and six months during it for either arm as an outcome measure. We reported these data as a demonstration of another marker of improved control. However, such an outcome is potentially limited as it is not known what constitutes a minimum clinically significant difference in dose changes to impact on a relevant outcome. The intervention arm of the Dalloul 2010 study involved participants receiving a once-daily oral dose of 175 mcg of vitamin K, but the authors gave no details of why this dose was chosen.

Quality of the evidence

We were only able to fully assess the quality of evidence for the Sconce 2007 study. We found the overall risk of bias to be low or unclear. There were no areas of the Sconce 2007 study that we deemed to have a high risk of bias. We were unable to assess the risk of bias of the Dalloul 2010 study.

Potential biases in the review process

There were insufficient numbers of included studies for us to complete a funnel plot to examine the risk of publication bias. However, we noted that the Dalloul 2010 was published in abstract only, which was confirmed through correspondence with the author (Dalloul 2013). It is possible that this occurred because there was no overall benefit shown and a full publication was not put forward. This introduces the possibility of publication bias although this is purely speculative. The fact that there are only two small included studies limits our conclusions.

Agreements and disagreements with other studies or reviews

We included the details of only one study that was published in a peer-reviewed journal in this review (Sconce 2007). However, we made note of two excluded studies during our selection process (Gebuis 2011; Rombouts 2007). Although both studies were randomised controlled trials evaluating the effect of vitamin K supplementation on vitamin K antagonists, neither antagonist was warfarin. In the Rombouts 2007 study, the authors carried out a double-blind, randomised, placebo-controlled trial on 200 participants from an anticoagulation clinic who used the vitamin K antagonist phenprocoumon. The authors concluded that supplementation of the vitamin K antagonist phenprocoumon with 100 mcg vitamin K improved stability of anticoagulant therapy. The Gebuis 2011 study randomised 400 participants initiated on the vitamin K antagonists acenocoumarol or phenprocoumon to receive placebo or 100, 150, or 200 mcg of vitamin K1 together with their treatment. The authors concluded that in participants starting vitamin K antagonists, supplementation with low-dose vitamin K1 resulted in an improvement of time that anticoagulation was within the therapeutic range. However, the authors noted that the differences between doses were small and questioned whether the improvement was likely to be of clinical relevance. They further considered whether this result would favour vitamin K supplementation had the population consisted of only participants with unstable anticoagulant control.

Authors' conclusions

Implications for practice

Based on the availability of only one full-peer reviewed trial (Sconce 2007), our results should be interpreted with caution. However,there may besome evidence that vitamin K supplementation improves the stability of the vitamin K antagonist warfarin in patients with existing INR instability. This would be consistent with other trials that examine the effect of vitamin K supplementation on the related vitamin K antagonists acenocoumarol and phenprocoumon. However, the risk of bias in several areas of the Sconce 2007 study was unclear. In addition, the study was relatively small. A further included study suggested no clear benefit of vitamin K supplementation, although this was based on data available in abstract form only (Dalloul 2010). Based on current evidence, concomitant use of vitamin K with warfarin cannot be recommended outside of the context of a trial setting.

Implications for research

Further larger, higher quality trials are required to evaluate if vitamin K supplementation improves the INR stability in patients taking warfarin. A greater benefit may be seen in those patients with existing poor INR control. Such patients with atrial fibrillation may also be suitable for newer novel direct thrombin inhibitors, such as dabigatran (NICE 2012). However, it is unclear whether these patients would benefit from vitamin K supplementation instead.

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Contributions of authors

Kamal R Mahtani (KM) wrote the first draft of this review with contributions from Carl Heneghan (CH), Nia Roberts (NR), and David Nunan (DN). Nia Roberts (NR) was responsible for carrying out the search strategy. All authors commented and made contributions to the final submitted review.

Declarations of interest

Kamal R Mahtani: nothing to declare.
Carl J Heneghan: nothing to declare.
David Nunan: nothing to declare.
Nia W Roberts: nothing to declare.

Differences between protocol and review

The authorship contributing to the full review.

Published notes

Characteristics of studies

Characteristics of included studies

Dalloul 2010

Methods	Prospective, randomised, double-blind, placebo-controlled study
Participants	Outpatient clinic records identified 50 participants on anticoagulation therapy with high variability in the INR levels. 30 were randomised into the study
Interventions	Oral vitamin K (175 mcg) daily versus placebo
Outcomes	INR levels were measured on a weekly basis for the first 4 weeks of the study. For a total of 6 months during follow-up visits, INR levels were subsequently measured and handled per goal-directed therapy. The primary outcome of the study was anticoagulation stability, defined as a reduction in the number of dose modifications during follow up
Notes	This was an abstract only. No further data were available after direct contact with the author

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was an abstract only. However, the authors described the study as being prospective, randomised, double-blind, and placebo-controlled
Allocation concealment (selection bias)	Unclear risk	This was an abstract only. No further information was available
Blinding of participants and personnel (performance bias)	Unclear risk	This was an abstract only. However, the authors described the study as being double-blind, although it was unclear who was blinded and how
Blinding of outcome assessment (detection bias)	Unclear risk	This was an abstract only. However, the authors described the study as being double-blind, although it was unclear who was blinded and how
Incomplete outcome data (attrition bias)	Unclear risk	This was an abstract only. 30 participants enrolled in the trial, although there were insufficient data to assess attrition
Selective reporting (reporting bias)	Unclear risk	This was an abstract only
Other bias	Unclear risk	This was an abstract only

Sconce 2007

Methods	Randomised controlled trial
Participants	Participants were recruited from the anticoagulation monitoring clinics at the Freeman Hospital and Royal Victoria Infirmary, Newcastle upon Tyne Hospitals National Health Service (NHS) Trust. Participants with atrial fibrillation anticoagulated with warfarin for thromboembolic prophylaxis who had a target international normalised ratio (INR) range of 2.0 to 3.0, had been taking warfarin for at least 9 months, and were defined as having unstable control were eligible to take part. The authors classified a participant as unstable if the SD of his/her INR values was greater than 0.5 and he/she had had at least 3 warfarin dose changes in the previous 6 months
Interventions	150 mcg oral vitamin K or placebo. Vitamin K (phytomenadione) (in 20:80 ethanol–deionised water solution) and matching placebo (20:80 ethanol–deionised water solution) were prepared as an oral solution at a concentration of 30 g/mL. Both formulations were dispensed to participants in a 200 mL dark-brown glass bottle (vitamin K is light-sensitive) with a 5 mL volume measuring cup every 4 weeks
Outcomes	The primary end point of the study was the SD of INR values in the 6-month study period compared with the same measurement in the 6 months immediately prior to the study. Secondary end points were the percentage of time at which the target INR value within 0.5 U was attained in each participant determined by the method of Azar 1994, the number of warfarin dose changes, and the number of participants who achieved an improved control of anticoagulation during the study compared with in the previous 6 months. Any adverse events, including the number and type of bleeding episodes and thromboembolic episodes including stroke, were recorded
Notes	70 participants with unstable control of anticoagulation consented to take part in the study Fasting plasma vitamin K concentrations were measured at baseline and in the 6-month study period

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Seventy patients were randomly allocated to 2 groups in a double-blinded fashion." No further information was provided
Allocation concealment (selection bias)	Unclear risk	There was no description of the allocation concealment technique used
Blinding of participants and personnel (performance bias)	Low risk	The authors made attempts to ensure that the participants were blinded to the intervention. Particpants receiving the active intervention or control were given vitamin K (phytomenadione) (in 20:80 ethanol–deionised water solution) or matching placebo (20:80 ethanol–deionised water solution). Both were dispensed to participants in a 200 mL dark-brown glass bottle (vitamin K is light-sensitive) with a 5 mL volume measuring cup every 4 weeks
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Seventy patients were randomly allocated to 2 groups in a double-blinded fashion" Quote: "All patients routinely attended their designated anticoagulation-monitoring service for the following 6 months, where their INR was checked and warfarin dosage adjusted if necessary using the Dawn Anticoagulation computer program (4S Information Systems, Milnthorpe, United Kingdom). This was performed independently by a pharmacist, thus preserving the study blindness." An attempt to preserve blinding had been clearly made by ensuring the pharmacist adjusting the dose remained independent. However, it was unclear if the researchers performing the outcome analysis were also blinded
Incomplete outcome data (attrition bias)	Low risk	Quote: "Seventy patients with unstable control of anticoagulation consented to take part in the study. Of these, 2 patients failed to complete it; 1 withdrew because of intervening illness, and the other died before completing the study. Neither case was related to the study. Both patients were later identified as having received placebo, and their results were not included in the final statistic analysis." Although the 2 participants that were enrolled but did not complete the study were accounted for, we were unclear why their data were not included in the final analysis. The authors did not formally state that they used an intention-to-treat principle
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes outlined in the methods section are presented and discussed in the results and discussion sections
Other bias	Unclear risk	Quote: "Both patients were later identified as having received placebo, and their results were not included in the final statistic analysis." This implied that analysis was not intention-to-treat

Footnotes

Characteristics of excluded studies

de Assis 2009

Reason for exclusion	There was no evidence of concomitant vitamin K supplementation when compared with a placebo arm

Ford 2007

Reason for exclusion	This was a prospective, open-label, cross-over study and was therefore excluded on the basis that the design did not meet our inclusion criteria

Ford 2008

Reason for exclusion	This was a review

Gebuis 2011

Reason for exclusion	This assessed vitamin K and acenocoumarol or phenprocoumon versus acenocoumarol or phenprocoumon alone (not warfarin)

JFP 2008

Reason for exclusion	This was a review

Kim 2001

Reason for exclusion	This was a pharmacokinetic study

Marongiu 1992

Reason for exclusion	This was not a RCT

NTR314 2005

Reason for exclusion	This appeared to be the trial registration of the Rombouts 2007 study

Patriquin 2011

Reason for exclusion	This was a review

Pedersen 1991

Reason for exclusion	This did not meet the inclusion criteria

Pengo 1993

Reason for exclusion	The aim was to assess the effect of vitamin K versus warfarin discontinuation in overcoagulated participants

Rombouts 2007

Reason for exclusion	This assessed the effect of vitamin K supplementation on the vitamin K antagonist phenprocoumon (not warfarin)

Shopnick 1998

Reason for exclusion	This did not meet the inclusion criteria

Sorano 1993

Reason for exclusion	This was not a RCT

Udall 1968

Reason for exclusion	This was not a RCT

Zuchinali 2012

Reason for exclusion	This was an analysis of a trial in which the INR was adjusted according to self-reported vitamin K intake

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

NCT00794755

Study name	A phase III pilot RCT (randomized, controlled trial) to assess the effectiveness of low dose vitamin K1 (200 micrograms per day) on improving anticoagulation control in unstable patients on warfarin
Methods	A double-blind, placebo-controlled, pilot RCT: phase 3
Participants	Unstable patients on warfarin
Interventions	Low-dose vitamin K1 (200 micrograms per day) versus placebo
Outcomes	Primary Anticoagulation control - point estimates (and standard deviations) for the following variables: per cent time in therapeutic range, standard deviation of INRs, number of INRs outside of therapeutic range, and number of dose changes Recruitment numbers - number of participants deemed eligible, number of participants solicited, number of participants screened, number of participants enrolled, and number of enrolled participants lost to follow-up Secondary Bleeding events - both major and minor as defined by the International Society on Thrombosis and Haemostasis (ISTH) criteria Recurrent thrombosis
Starting date	November 2008
Contact information	-
Notes	We were unable to find the published trial for this registration. Clinicaltrials.gov reports: "No study results posted on ClinicalTrials.gov for this study" Website accessed 12th February 2014

NCT00990158

Study name	A multicentre study of low dose oral vitamin K for INR control in patients receiving warfarin
Methods	The proposed pilot study is a multicentre, placebo-controlled, randomised trial with an additional pilot mechanistic study
Participants	Patients receiving warfarin
Interventions	Participants will receive a daily dose of 150 micrograms of vitamin K or a matching placebo medication for a total of 7 months
Outcomes	The primary outcome is a simple comparison of mean TTRs in the low-dose vitamin K and placebo participants
Starting date	July 2010
Contact information	-
Notes	Website accessed 12th February 2014

Footnotes

Summary of findings tables

Additional tables

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Studies awaiting classification

Ongoing studies

NCT00794755

Unpublished data only

NCT00794755. A phase III pilot RCT (randomized, controlled trial) to assess the effectiveness of low dose vitamin K1 (200 micrograms per day) on improving anticoagulation control in unstable patients on warfarin. http://clinicaltrials.gov/show/NCT00794755.

NCT00990158

Unpublished data only

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Other published versions of this review

Classification pending references

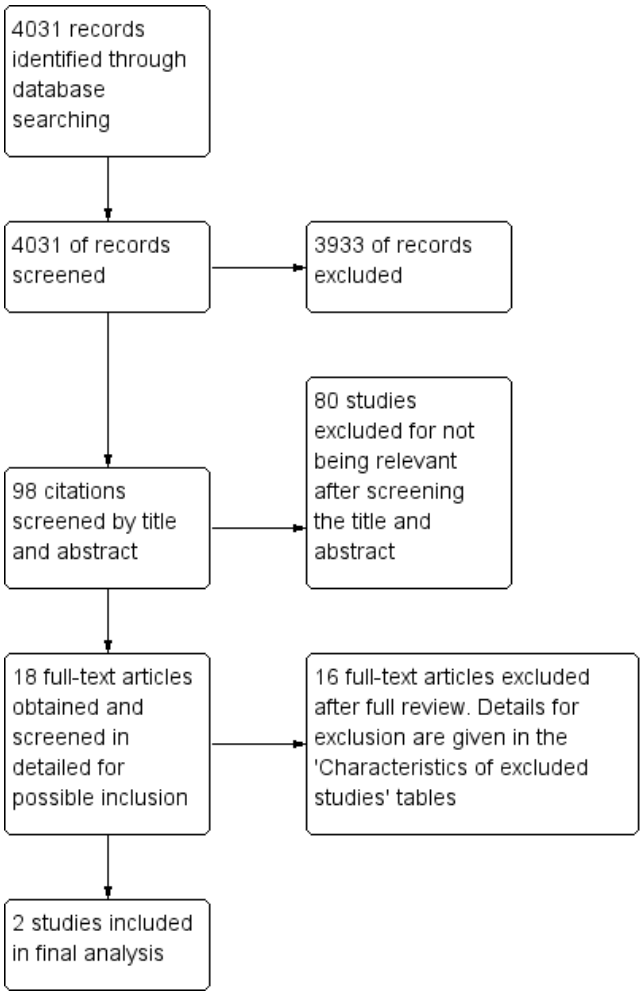
Data and analyses

1 Other markers of improved anticoagulation control

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Other markers of improved anticoagulation control	1	68	Odds Ratio(M-H, Fixed, 95% CI)	6.19[1.22, 31.26]

Figures

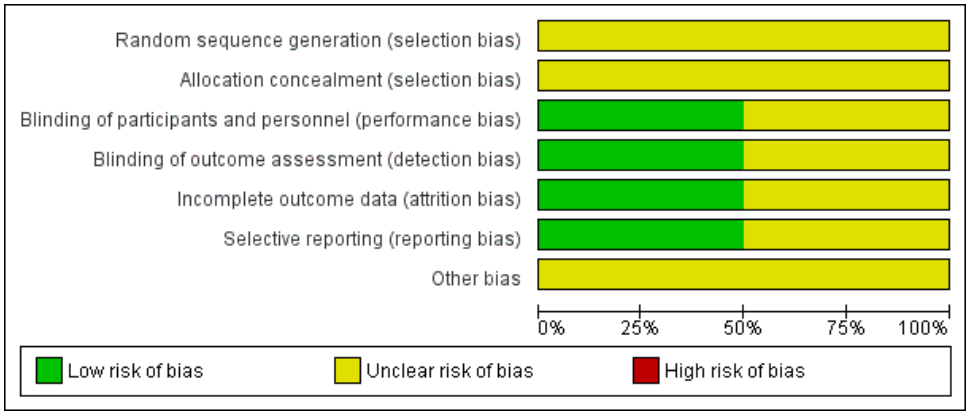
Figure 1



Caption

Study flow diagram

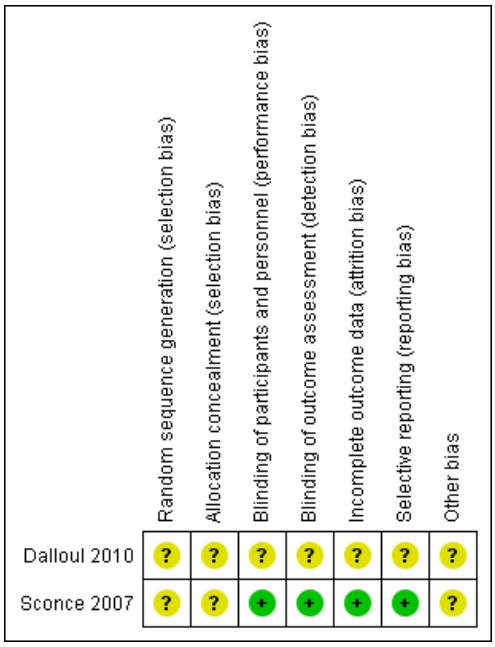
Figure 2



Caption

'Risk of bias' graph: Review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies

Figure 3



Caption

'Risk of bias' summary: Review authors' judgements about each 'Risk of bias' item for each included study

Sources of support

Internal sources

- No sources of support provided

External sources

- Kamal Mahtani (KM) is an NIHR-funded academic clinical lecturer in General Practice, UK

Feedback

Appendices

1 Search strategy

Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE (R) (OvidSP) (1946 to 25 February 2014)

1. Warfarin/
2. (Warfarin or Marevan or Jantoven or Coumadin or Orfarin).mp.
3. Coumarins/
4. ((Oral* adj3 (Anticoagula* or Anti-coagula*)) or coumarin*).ti,ab.
5. 1 or 2 or 3 or 4
6. Vitamin K/
7. (Vitamin K or Menadiol or Menadione or Menaquinone or Menatetrenone or Phytonadione or Methylphytyl or Naphthoquinone or Phylloquinone or Phytomenadione).mp.
8. 6 or 7
9. 5 and 8
10. randomized controlled trial.pt.
11. controlled clinical trial.pt.
12. randomized.ab.
13. placebo.ab.
14. drug therapy.fs.
15. randomly.ab.
16. trial.ab.
17. groups.ab.
18. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

19. exp animals/ not human/

20. 18 not 19

21. 9 and 20

Embase (OvidSP) (1974 to week 8 of 2014)

1. *Warfarin/

2. (Warfarin or Marevan or Jantoven or Coumadin or Orfarin).mp.

3. *anticoagulant agent/po [Oral Drug Administration]

4. *coumarin anticoagulant/

5. ((Oral* adj3 (Anticoagula* or Anti-coagula*)) or coumarin*).ti,ab.

6. 1 or 2 or 3 or 4 or 5

7. exp *vitamin K group/

8. (Vitamin K or Menadiol or Menadione or Menaquinone or Menatetrenone or Phytonadione or Methylphytyl or Naphthoquinone or Phylloquinone or Phytomenadione).mp.

9. 7 or 8

10. 6 and 9

11. random*.tw. or placebo*.mp. or double-blind*.mp.

12. 10 and 11

Cochrane Central Register of Controlled Trials (CENTRAL) & NHS Economics Evaluations Database (via The Cochrane Library, Wiley) (Issue 2, 2014)

#1 Warfarin or Marevan or Jantoven or Coumadin or Orfarin:ti,ab,kw (Word variations have been searched)

#2 MeSH descriptor: [Coumarins] this term only

#3 MeSH descriptor: [Anticoagulants] this term only

#4 ((Oral* near/3 (Anticoagula* or Anti-coagula*)) or coumarin*):ti,ab,kw (Word variations have been searched)

#5 antiocoagula* or anti-coagula*:ti (Word variations have been searched)

#6 ((variab* or stable* or stability or unstable* or instable* or instability or control*) near (anticoagula* or anti-coagula*)):ti,ab,kw (Word variations have been searched)

#7 #1 or #2 or #3 or #4 or #5 or #6

#8 "Vitamin K*" or Menadiol or Menadione or Menaquinone or Menatetrenone or Phytonadione or Methylphytyl or Naphthoquinone or Phylloquinone or Phytomenadione:ti,ab,kw (Word variations have been searched)

#9 #7 and #8

Science Citation Index Expanded™ & Conference Proceedings Citation Index - Science (Web of Science™) (1945 to 27 February 2014)

#9	1,026	#8 AND #7 Indexes=SCI-EXPANDED, CPCI-S Timespan=1945-2014
#8	2,169,877	TS=(random* OR blind* OR allocat* OR assign* OR trial* OR placebo* OR crossover* OR cross-over*)
#7	3,073	#6 AND #5
#6	20,124	**TOPIC:** ("Vitamin K*" or Menadiol or Menadione or Menaquinone or Menatetrenone or Phytonadione or Methylphytyl or Naphthoquinone or Phylloquinone or Phytomenadione)
#5	44,648	#4 OR #3 OR #2 OR #1
#4	2,682	TS=((((variab* or stable* or stability or unstable* or instable* or instability or control*) NEAR/5 (anticoagula* or anti-coagula*))))
#3	719	**TITLE:** ((antiocoagula* or anti-coagula*))
#2	27,042	**TOPIC:** ((((Oral* NEAR/3 (Anticoagula* or Anti-coagula*)) or coumarin*)))
#1	20,094	**TOPIC:** ((Warfarin or Marevan or Jantoven or Coumadin or Orfarin))

Search terms for trial registries & OpenGrey

“Vitamin K” or Menadiol or Menadione or Menaquinone or Menatetrenone or Phytonadione or Methylphytyl or Naphthoquinone or Phylloquinone or Phytomenadione

Graphs

1 - Other markers of improved anticoagulation control

1.1 Other markers of improved anticoagulation control