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Optimal loading dose of warfarin for the initiation of oral anticoagulation.
Cochrane Database of Systematic Reviews 2012, Issue 12. Art. No.: CD008685.
DOI: [10.1002/14651858.CD008685.pub2](https://doi.org/10.1002/14651858.CD008685.pub2).

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TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	5
OBJECTIVES	5
METHODS	5
RESULTS	7
Figure 1.	7
Figure 2.	8
Figure 3.	9
Figure 4.	11
Figure 5.	13
Figure 6.	15
DISCUSSION	16
AUTHORS' CONCLUSIONS	18
ACKNOWLEDGEMENTS	18
REFERENCES	19
CHARACTERISTICS OF STUDIES	22
DATA AND ANALYSES	33
Analysis 1.1. Comparison 1: 5 mg versus 10 mg, Outcome 1: INR in-range by day 5: 5mg v 10mg	34
Analysis 1.2. Comparison 1: 5 mg versus 10 mg, Outcome 2: Single INR measure	34
Analysis 1.3. Comparison 1: 5 mg versus 10 mg, Outcome 3: Consecutive INR measures	34
ADDITIONAL TABLES	34
APPENDICES	40
WHAT'S NEW	41
HISTORY	41
CONTRIBUTIONS OF AUTHORS	41
DECLARATIONS OF INTEREST	41
SOURCES OF SUPPORT	41
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	41
INDEX TERMS	42

[Intervention Review]

Optimal loading dose of warfarin for the initiation of oral anticoagulation

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Editorial group: Cochrane Heart Group.

Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 9, 2021.

Citation: Mahtani KR, Heneghan CJ, Nunan D, Bankhead C, Keeling D, Ward AM, Harrison SE, Roberts NW, Hobbs FR, Perera R. Optimal loading dose of warfarin for the initiation of oral anticoagulation. *Cochrane Database of Systematic Reviews* 2012, Issue 12. Art. No.: CD008685. DOI: [10.1002/14651858.CD008685.pub2](https://doi.org/10.1002/14651858.CD008685.pub2).

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ABSTRACT

Background

Warfarin is used as an oral anticoagulant. However, there is wide variation in patient response to warfarin dose. This variation, as well as the necessity of keeping within a narrow therapeutic range, means that selection of the correct warfarin dose at the outset of treatment is not straightforward.

Objectives

To assess the effectiveness of different initiation doses of warfarin in terms of time in-range, time to INR in-range and effect on serious adverse events.

Search methods

We searched CENTRAL, DARE and the NHS Health economics database on *The Cochrane Library* (2012, Issue 4); MEDLINE (1950 to April 2012) and EMBASE (1974 to April 2012).

Selection criteria

All randomised controlled trials which compared different initiation regimens of warfarin.

Data collection and analysis

Review authors independently assessed studies for inclusion. Authors also assessed the risk of bias and extracted data from the included studies.

Main results

We identified 12 studies of patients commencing warfarin for inclusion in the review. The overall risk of bias was found to be variable, with most studies reporting adequate methods for randomisation but only two studies reporting adequate data on allocation concealment. Four studies (355 patients) compared 5 mg versus 10 mg loading doses. All four studies reported INR in-range by day five. Although there was notable heterogeneity, pooling of these four studies showed no overall difference between 5 mg versus 10 mg loading doses (RR 1.17, 95% CI 0.77 to 1.77, $P = 0.46$, $I^2 = 83\%$). Two of these studies used two consecutive INRs in-range as the outcome and showed no difference between a 5 mg and 10 mg dose by day five (RR 0.86, 95% CI 0.62 to 1.19, $P = 0.37$, $I^2 = 22\%$); two other studies used a single INR in-range

as the outcome and showed a benefit for the 10 mg initiation dose by day 5 (RR 1.49, 95% CI 1.01 to 2.21, $P = 0.05$, $I^2 = 72\%$). Two studies compared a 5 mg dose to other doses: a 2.5 mg initiation dose took longer to achieve the therapeutic range (2.7 versus 2.0 days; $P < 0.0001$), but those receiving a calculated initiation dose achieved a target range quicker (4.2 days versus 5 days, $P = 0.007$). Two studies compared age adjusted doses to 10 mg initiation doses. More elderly patients receiving an age adjusted dose achieved a stable INR compared to those receiving a 10 mg initial dose (and Fennerty regimen). Four studies used genotype guided dosing in one arm of each trial. Three studies reported no overall differences; the fourth study, which reported that the genotype group spent significantly more time in-range ($P < 0.001$), had a control group whose INRs were significantly lower than expected. No clear impacts from adverse events were found in either arm to make an overall conclusion.

Authors' conclusions

The studies in this review compared loading doses in several different situations. There is still considerable uncertainty between the use of a 5 mg and a 10 mg loading dose for the initiation of warfarin. In the elderly, there is some evidence that lower initiation doses or age adjusted doses are more appropriate, leading to fewer high INRs. However, there is insufficient evidence to warrant genotype guided initiation.

PLAIN LANGUAGE SUMMARY

The optimal warfarin dose for patients beginning therapy

Warfarin is commonly prescribed to prevent blood clots in patients with medical conditions such as atrial fibrillation, heart valve replacement or previous blood clots. Warfarin is an effective treatment which has been used for many years but needs to be closely monitored, especially at the beginning of treatment, as there is a wide variation in response to dose. Monitoring of the response to dose is done using an International Normalized Ratio (INR) and it is important that patients remain within a narrow range (typically 2 to 3 INR) due to the need to balance the goal of preventing blood clots with the risk of causing excessive bleeding.

This review included 12 randomised controlled trials comparing different warfarin doses given to patients beginning warfarin treatment. Most of the studies had a high risk of bias so the results were interpreted with caution.

Those trials that were included compared loading doses in several different situations. The review authors divided the trials into four categories, 5 mg versus 10 mg initial doses (four studies), 5 mg versus other doses (two studies), 5 mg or 10 mg versus age adjusted doses (two studies), 5 mg or 10 mg versus genotype adjusted doses (four studies).

The review authors concluded that there is still considerable uncertainty between the use of a 5 mg and a 10 mg loading dose for the initiation of warfarin. In the elderly, there is some evidence that lower initiation doses or age adjusted doses are more appropriate. However, there is insufficient evidence to warrant genotype adjusted dosing. We also found no data to suggest that any one method was safer than another.

SUMMARY OF FINDINGS

Summary of findings 1. 5 mg versus 10 mg for the initiation of oral anticoagulation

5 mg versus 10 mg for the initiation of oral anticoagulation

Patient or population: patients with the initiation of oral anticoagulation

Settings:

Intervention: 5 mg versus 10 mg

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	5 mg versus 10 mg				
All studies	Study population		RR 1.17 (0.77 to 1.77)	352 (4 studies)	⊕⊕⊕⊕ very low 1,2,3,4,5,6,7,8	
	571 per 1000	668 per 1000 (440 to 1000)				
	Medium risk population					
	593 per 1000	694 per 1000 (457 to 1000)				
Single INR measure	Study population		RR 1.49 (1.01 to 2.21)	250 (2 studies)	⊕⊕⊕⊕ very low 1,2,3,5,7,8	
	504 per 1000	751 per 1000 (509 to 1000)				
	Medium risk population					
	565 per 1000	842 per 1000 (571 to 1000)				
Consecutive INR measures	Study population		RR 0.86 (0.62 to 1.19)	102 (2 studies)	⊕⊕⊕⊕ very low 1,2,3,4,7,8	
	714 per 1000	614 per 1000 (443 to 850)				
	Medium risk population					
	696 per 1000	599 per 1000				

(432 to 828)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **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.

- 1 Method of allocation concealment not described by Crowther 1999, Harrison 1997 or Quiroz 2006.
- 2 Worse-case-scenario modelling used for incomplete outcome data by Crowther 1999. Handling of incomplete outcome data not described by Harrison 1997.
- 3 No double blinding (patient and physician) by Crowther 1999, Harrison 1997 or Quiroz 2006.
- 4 No adverse outcomes data reported by Crowther 1999.
- 5 Selective reporting by Kovacs 2003 (i.e. time to stable INR - 2 days not reported, results report patients therapeutic by day 5 though outcome described as on day 5).
- 6 Studies comparing 5 mg and 10 mg initiation doses of warfarin either reported single INR in-range or two consecutive INR in-range.
- 7 There was variation in the time frames over which serious adverse effects were assessed.
- 8 Insufficient data to pool outcomes by type of loading dose prevented assessment of publication bias and selective reporting of studies.

BACKGROUND

Description of the condition

Oral anticoagulants are used in a number of clinical conditions to prevent the blood clotting inappropriately. They are effective for the prevention and treatment of thromboembolic events ([Stroke 1994](#)) and in other conditions, including deep vein thromboses (DVT), pulmonary emboli (PE) ([Barritt 1960](#)), mitral and aortic valve replacements (MVR, AVR) ([Kearon 2008](#); [Whitlock 2012](#)) and atrial fibrillation (AF) ([AF III 1996](#); [Atrial Pooled Data 1994](#); [Boston AF Trial 1990](#); [Janes 2009](#)), together with occasional use in patients with heart failure and those with peripheral and cerebral vascular disease. However, the National Institute for Health and Clinical Excellence (UK) have estimated that of the 355,000 patients with AF and at high risk of stroke, only 189,000 (53%) were on warfarin ([NHS Improvement 2009](#)). Appropriate use of oral anticoagulants can substantially reduce the burden of disease associated with these conditions. For example, analysis of pooled data from five clinical trials showed a reduction in annual stroke rate from 4.5% to 1.4% for patients assigned to adjusted-dose warfarin. The absolute risk difference means 31 ischaemic strokes will be prevented each year for every 1000 patients treated ([Atrial Pooled Data 1994](#)).

Description of the intervention

Warfarin is an oral vitamin K antagonist that inhibits the activity of clotting factors II, VII and X ([Hirsh 2001](#)). The dose of warfarin is variable and safe and effective monitoring of therapy is undertaken using the International Normalized Ratio (INR), developed to reduce problems caused by variability in the sensitivity of different commercial sources of thromboplastin to the vitamin K dependent blood coagulation factor VII ([Ansell 2004](#)). An INR between 2.0 and 3.0 is generally accepted, with the exception of valve replacements where a higher INR of between 2.5 and 3.5 or 3.0 and 4.0 is usually recommended ([Ansell 2003](#); [Ansell 2004](#)). Although warfarin is an effective antithrombotic agent, the therapeutic range is narrow due to the need to balance reducing thrombotic events with increased risk of bleeding ([Schulman 2008](#)). Some conditions (for example DVT) require the establishment of effective anticoagulation quickly to reduce harms whilst reducing concomitant treatments such as heparin. In other conditions, such as outpatient diagnosis of AF, the time to establish the therapeutic range is not as crucial ([Darkow 2005](#)). An appropriate time to a therapeutic INR is important as rapid over-anticoagulation can lead to bleeding, while a delayed therapeutic INR could increase the risk of thrombosis.

How the intervention might work

There is a wide variation in the individual dose response to warfarin. Many factors influence this individual response. These include increasing age, genetic factors and environmental factors such as drugs, diet and various disease states ([Ansell 2004](#)). Because of this individual variation, careful monitoring is required, especially in the initiation phase of treatment. It is particularly important to optimise the time in therapeutic range as this has been shown to predict adverse events in patients ([Wan 2008](#)). Different methods of initiating warfarin have been tried in clinical practice with the aim of establishing the therapeutic window efficiently without causing adverse effects. Initial doses of warfarin include 10 mg ([Harrison 1997](#)), 5 mg ([Harper 2005](#)), 2.5 mg ([Ageno 2001](#)) and, in the elderly, lower doses such as 1 mg ([Baglin 2007](#)).

In addition, initiation dosing can be done using protocols such as Fennerty's, which relies on consecutive daily INRs over the first four days to predict the next day's warfarin dose ([Roberts 1999](#)). There has also been considerable interest in genotype guided warfarin initiation ([Wadelius 2009](#)). In particular, polymorphisms in the gene coding of the enzyme CYP2C9 significantly alter the metabolism of warfarin, such that carriers of alleles CYP2C9*2 and CYP2C9*3 may have slower metabolism of warfarin and potentially a greater risk of bleeding, particularly during initiation; they subsequently require lower maintenance doses of warfarin ([Shurin 2008](#)).

Why it is important to do this review

The use of oral anticoagulants such as warfarin has increased substantially over the last decade, particularly within the context of an ageing population ([Fitzmaurice 2005](#); [van Walraven 2009](#)). In 2001 it was estimated that 470,000 patients in the UK were taking anticoagulation treatment ([Fitzmaurice 2001](#)). The UK National Institute of Clinical Excellence (NICE) currently estimates a benchmark rate of 1.4% of the UK population (approximately 840,000 people) requiring long-term anticoagulation treatment. This is based on epidemiological data which estimated the prevalence of the three main conditions requiring anticoagulation therapy as AF 1%, DVT 0.2% and heart valve replacements 0.2% ([NICE 2010](#)). Balancing the need for effective anticoagulation with reduced time to therapeutic INR without concomitant increases in adverse events is important. Selection of the right warfarin dose at the outset is not straightforward, and a systematic review of evidence is needed to determine the optimal strategy.

OBJECTIVES

To assess the effectiveness in reaching a target INR from different loading dose regimens of warfarin in terms of time in-range, time to INR in-range and effect on serious adverse events.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials of different loading dose regimens in patients aged 18 years and over commencing anticoagulation with warfarin.

Types of participants

Adult patients commencing anticoagulation with warfarin irrespective of condition, for example AF, DVT, PE, heart valve replacement, post-operative venous thromboembolism prophylaxis.

Types of interventions

Comparisons of the initiation of different warfarin regimens, for example 2.5 mg, 5 mg, 10 mg, age adjusted regimens, genotype adjusted regimens.

If feasible, comparisons of different dose adjusting interventions, for example Fennerty's, fixed dose and any other dose adjusting interventions.

Types of outcome measures

Primary outcomes

1. Time to first INR in-range
2. Time to two consecutive INRs in-range
3. Proportion of INRs in-range from day of initiation
4. Percentage of time INR in-range

Secondary outcomes

1. Proportion of supratherapeutic INRs and subtherapeutic INRs
2. Vitamin K given
3. Serious adverse events within 28 days of warfarin initiation: fatal or life-threatening bleeds, blood transfusions or hospitalisation, DVT, PE, other thromboembolic events
4. Quality of life

Search methods for identification of studies

Electronic searches

Searches were carried out up to and including the 20th April 2012. We searched the Cochrane Central Register of Controlled Trials (CENTRAL), Database of Reviews of Effectiveness (DARE) and the NHS Health Economics Database on *The Cochrane Library* (2012, Issue 4); MEDLINE (1950 to April 2012); and EMBASE (1974 to April 2012). See [Appendix 1](#) for detailed search strategies. The Cochrane sensitive-maximising RCT filter was used when searching MEDLINE and EMBASE ([Lefebvre 2011](#)).

No date or language restrictions were applied.

Searching other resources

We performed citation searches and reviewed the references of all full text papers retrieved. We also contacted experts in the field where relevant. We searched for any ongoing trials that are registered with the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (<http://apps.who.int/trialsearch/>) and the Current Controlled Trials Register (www.controlled-trials.com/). Where necessary, we also contacted authors of relevant studies.

Data collection and analysis

Selection of studies

Four review authors independently assessed relevant titles (KM, DN, SH, CB). Where necessary, abstracts of all studies identified by the initial search were reviewed and clearly irrelevant studies were excluded. The full texts of articles selected on the basis of title and abstract as well as any articles where there was uncertainty were obtained. Four review authors (KM, DN, SH, CB) independently reviewed the studies for final inclusion or exclusion. Disagreements were resolved by discussion and, when necessary, with a further author (CH). In cases where inclusion or exclusion was still unclear, we attempted to contact the study author for clarification.

Data extraction and management

Data extraction forms specifically designed for this review were used to extract data on participants, interventions and outcomes. Trial results were extracted independently by four review authors (KM, DN, SH, CB). Differences between authors' abstraction results were resolved by discussion and, when necessary, in consultation

with a further review author (CH). Where data were insufficiently reported in the published paper we wrote to the original authors for clarification and further information.

Assessment of risk of bias in included studies

Three review authors (KM, DN, SH) independently assessed the risk of bias of all included studies. The specific aspects assessed were: method of randomisation, allocation concealment, blinding of outcome assessors, treatment of incomplete outcome data, selective reporting, follow up and other potential sources of bias. Risk of bias was reported using the Cochrane Collaboration's tool for assessing risk of bias ([Higgins 2011](#)).

Measures of treatment effect

For dichotomous outcomes we compared different regimens using relative risks (RR) and calculated the 95% confidence intervals (CIs). For continuous outcomes we used weighted mean difference (WMD) with 95% CI to summarise the pooled effect. Where only a single study was included in a subgroup, we have presented the outcomes as mean differences (MD).

Unit of analysis issues

Unit of analysis issues were not anticipated and the 12 studies included in the review did not use non-standard designs (that is cross-over or cluster randomised designs).

Dealing with missing data

We aimed to conduct our analysis using the intention-to-treat principle. Where data were insufficiently reported in the published paper we wrote to the original authors for clarification and further information. We analysed only the available data and discussed the impact of the missing data on our findings.

Assessment of heterogeneity

Where we pooled data we used the I^2 statistic to measure statistical heterogeneity for each outcome. Where no heterogeneity was present, we used a fixed-effect model meta-analysis and where substantial heterogeneity (I^2 above 50%) was detected, we looked for the direction of the effect and used a random-effects model analysis.

Assessment of reporting biases

A funnel plot was generated to examine the possibility of publication bias for the four studies comparing 5 mg versus 10 mg loading regimens. Other potential reporting biases were addressed in the discussion.

Data synthesis

We pooled data using a random-effects model. We looked for consistency in the direction of the effect. We performed a sensitivity analysis removing each study one at a time to see which study contributed most to the heterogeneity.

Subgroup analysis and investigation of heterogeneity

Although there was considerable heterogeneity across the included studies, we grouped them into four clinically relevant categories: 5 mg versus 10 mg; 5 mg versus other doses; 5 mg or 10 mg versus an age adjusted loading dose; and 5 mg or 10g versus a genotype loading dose.

Sensitivity analysis

If heterogeneity was found, we examined the methodological and clinical characteristics of the included trials and gave a narrative explanation as to what impact any difference may have had on the results, or the likely explanation for the heterogeneity.

RESULTS

Description of studies

Results of the search

A total of 1600 references were obtained from the searches of which 19 were identified as possibly relevant from their titles and

abstracts. These were requested as full text and independently assessed by review authors. Seven of these papers were excluded (see 'Characteristics of excluded studies' table). One of the papers was a report in German of a study which was also described in English (Harrison 1997). Citation searching did not identify any papers which had not been previously identified by the searches. Figure 1 is a flow diagram of our search results.

Figure 1. Study flow diagram.

Included studies

A total of 12 studies met the inclusion criteria (Ageno 2001; Anderson 2007; Burmester 2011; Caraco 2008; Crowther 1999; Gedge 2000; Harrison 1997; Hillman 2005; Kovacs 2003; Quiroz 2006; Roberts 1999; Shine 2003) ,see Characteristics of included studies.

Excluded studies

A total of seven studies which were randomised controlled trials of different loading dose or different regimens in patients aged 18 years and over commencing anticoagulation with warfarin were excluded from the review. One was excluded because the outcome measures were not comparable to the included studies in the

review (Iguchi 1994), one was excluded because the therapeutic INR was not comparable (Schulman 1984) and one was excluded because it was a cross-over study of healthy participants (Hameed 2008). Two studies were excluded because they used derivatives of warfarin. The Van Den 2002 study used acenocoumarol while the van Schie 2011 study examined both acenocoumarol and phenprocoumon. A further two studies were excluded because they compared standard nomograms with empirical dosing (Doecke 1991; Kovacs 1999).

Risk of bias in included studies

We assessed bias using Higgins 2011a as our reference. For all studies we assessed the risk of bias in six areas: method of randomisation, allocation concealment, blinding, treatment of incomplete outcome data, selective reporting and other potential sources of bias. Studies were categorised in each area as being yes, no, or unclear (see 'Characteristics of included studies' table). None of the studies were deemed to be of high quality (that is achieving yes in all areas). We presented the results of this assessment in risk of bias tables as well as a risk of bias graph (Figure 2) and risk of bias summary (Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
Ageno 2001	+	?	-	-	+	-
Anderson 2007	+	?	+	+	+	-
Burmester 2011	+	?	+	?	+	?
Caraco 2008	-	?	?	-	+	?
Crowther 1999	+	?	-	?	+	?
Gedge 2000	?	?	?	-	+	?
Harrison 1997	+	?	-	-	+	?
Hillman 2005	+	+	-	+	+	?
Kovacs 2003	+	+	+	+	?	+
Quiroz 2006	+	?	-	+	+	+
Roberts 1999	-	-	-	-	+	
Shine 2003	+	-	?	-	+	?

Allocation

The Hillman 2005 study reported that on recruitment patient data were entered into a database which contained a concealed randomisation table. The Kovacs 2003 study reported that allocation was not known by the investigators and was contained in opaque sealed envelopes. The remaining included studies were either rated as having an unclear or high risk of bias for allocation concealment.

Blinding

Only one study (Kovacs 2003) reported that double-blinding (physician and patient) was used.

Incomplete outcome data

Three studies (Anderson 2007; Hillman 2005; Kovacs 2003) did an intention-to-treat analysis and one study (Crowther 1999) used a 'worst-case scenario' model.

Selective reporting

All the studies assessed relevant outcomes and reported these for both groups. However, there was concern whether a single INR measure is adequate to assess mean time to INR in-range or whether two consecutive INR measures were more appropriate

Other potential sources of bias

Other potential sources of bias included: imbalance of demographic and clinical characteristics between groups at baseline (Anderson 2007; Caraco 2008; Hillman 2005) and a disproportionate exclusion of patients from the study when the dose differed from the protocol (Ageno 2001). In the Burmester 2011 study there appeared to be an imbalance in drop-outs between groups (clinical parameters 25% versus genotype+clinical parameters 15%).

Effects of interventions

See: **Summary of findings 1** 5 mg versus 10 mg for the initiation of oral anticoagulation

All patients included in the studies were newly initiated on warfarin. In one study (Burmester 2011) eligible patients also included those restarting therapy without a documented stable warfarin dose available in the medical record. In 10 studies the recruited patients had a target INR in the range of 2.0 to 3.0 (Anderson 2007; Caraco 2008; Crowther 1999; Gedge 2000; Harrison 1997; Hillman 2005; Kovacs 2003; Quiroz 2006; Roberts 1999; Shine 2003). In the Burmester 2011 study the target INR range was between 2 and 3.5. In two studies the inclusion criteria were patients with DVT or PE only (Kovacs 2003; Quiroz 2006). In Kovacs 2003 the primary end point of the study was time in days to a therapeutic INR (> 1.9). In the Quiroz 2006 study the primary end point was defined as the number of days necessary to achieve two consecutive INRs > 1.9 . One further study included patients after heart valve replacement, with a target INR of 1.5 to 2.6 (Ageno 2001).

Trials varied in relation to the loading doses compared and the dose protocols that were used. The warfarin loading doses were: 5 mg versus 10 mg (four studies) (Crowther 1999; Harrison 1997; Kovacs

2003; Quiroz 2006); 5 mg versus 2.5 mg (one study) (Ageno 2001); 5 mg versus dose adjusted for clinical factors (one study) (Shine 2003); 10 mg versus dose adjusted for age (two studies) (Gedge 2000; Roberts 1999); 5 mg versus dose adjusted for genotype (two studies) (Caraco 2008; Hillman 2005), and 10 mg versus dose adjusted for genotype (one study) (Anderson 2007). The Burmester 2011 study used the Marshfield pharmacogenetic models for predicting therapeutic warfarin dose. These regression models use multiple relevant clinical parameters with or without genotype information to predict warfarin dose.

Studies used a variety of initiation of dosing protocols in both arms of the trials (Table 1). In six studies INR was measured daily up to day five (Ageno 2001; Caraco 2008; Crowther 1999; Harrison 1997; Quiroz 2006; Shine 2003), and in three studies INR was measured at times pre-specified by the dosing protocol (Anderson 2007; Hillman 2005; Kovacs 2003). The Burmester 2011 study differed from others in that patients in both arms of the trial were started on an individually calculated dose of warfarin based on an algorithm that either did or did not include genetic information. Follow-up varied from five to 90 days. Outcomes measured included: time to INR in-range, percentage time in-range, percentage in-range at day five, percentage with an INR above range, time to reach 'stable' anticoagulation (as defined by each study), percentage with an INR > 4.0 to 5.0, proportion of serious adverse events such as serious bleeding, absolute prediction error relative to therapeutic dose, VTE and death. Table 2 summarises these results.

Although there was considerable heterogeneity across the 12 studies in terms of design quality, loading dose protocols, patient population, outcome measures, and length of follow-up, we grouped them into four clinically relevant categories: 5 mg versus 10 mg (Crowther 1999; Harrison 1997; Kovacs 2003; Quiroz 2006); 5 mg versus other doses (Ageno 2001; Shine 2003); age adjusted (Gedge 2000; Roberts 1999); and genotype loading dose (Anderson 2007; Burmester 2011; Caraco 2008; Hillman 2005).

5 mg versus 10 mg loading dose

Four studies (355 participants) compared 5 mg versus 10 mg loading doses (Crowther 1999; Harrison 1997; Kovacs 2003; Quiroz 2006). Table 1 illustrates the nomograms used for dosing, which varied across the studies. All four studies reported INR in-range by day five (Figure 4) and meta-analysis (Analysis 1.1) revealed no overall difference between 10 mg and 5 mg loading doses (RR 1.17, 95% CI 0.77 to 1.77, $P = 0.46$). However, we interpreted these results with caution as we noted high heterogeneity ($I^2 = 83\%$). Sensitivity analysis by removing each study revealed that the Kovacs 2003 study contributed the most heterogeneity. Once excluded, the remaining studies confirmed no overall difference between 10 mg and 5 mg (RR 0.98, 95% CI 0.73 to 1.32, $P = 0.90$, $I^2 = 44\%$). A funnel plot of these trials suggested there was an insufficient number of trials to attribute this to publication bias. In the two studies that used single INR measures (Harrison 1997; Kovacs 2003) a loading dose of 10 mg led to more patients in-range on day five with weak evidence that this was significant, although heterogeneity remained high (RR 1.49, 95% CI 1.01 to 2.21, $P = 0.05$, $I^2 = 72\%$) (Analysis 1.2). Kovacs 2003, also reported that the mean time to being in-range was significantly shorter using a 10 mg than a 5 mg loading dose (5.6 versus 4.2 days, $P < 0.001$) (Table 2).

Figure 4. Proportion of Patients with a therapeutic INR from day of initiation (5 mg versus 10 mg).

Figure 4. (Continued)

In contrast, in the two studies that required two consecutive INRs at day five ([Crowther 1999](#); [Quiroz 2006](#)) a 10 mg loading dose did not lead to more patients in-range on day five (RR 0.86, 95% CI 0.62 to 1.19, $P = 0.37$, $I^2 = 22\%$) ([Analysis 1.3](#)). In addition, in the [Quiroz 2006](#) study the authors reported that the 5 mg group achieved therapeutic INRs more often during days 6 to 14 (raw data not available), reporting no difference in median time to two consecutive INRs being in-range ([Table 2](#)).

[Kovacs 2003](#) and [Quiroz 2006](#) chose an INR ≥ 5.0 to be supratherapeutic and found that the proportion of patients with this was no different between the two dosing groups ([Table 2](#)).

5 mg versus other doses

Two studies (322 participants) compared a 5 mg loading dose with 2.5 mg ([Ageno 2001](#)) and 5 mg with a calculated dose ([Shine 2003](#)). In the [Ageno 2001](#) study in heart valve replacement patients (INR target 1.5 to 2.6), patients receiving 2.5 mg took longer to achieve the therapeutic range (2.7 versus 2.0 days, $P < 0.0001$) but were less likely to have an INR > 2.6 (26% versus 42%, $P < 0.05$) and had fewer days with INR > 2.6 (average 0.9 versus 0.45 days, $P = 0.003$).

[Shine 2003](#) compared 5 mg with a calculated dose that took account of age, weight, serum albumin and active malignancy.

Patients receiving the calculated dose achieved the target range quicker (4.2 days versus 5 days, $P = 0.007$) but there was no difference in the proportion achieving INR in-range on or before day six: 77% calculated dose compared to 63% in the 5 mg dose (RR 1.22, 95% CI 0.88 to 1.70, $P = 0.24$) ([Table 2](#)).

Age adjusted

Two studies (192 participants) compared loading doses adjusted for age with Fennerty's protocol ([Roberts 1999](#)) or a modified Fennerty protocol ([Gedge 2000](#)) in the standard arm.

In the [Roberts 1999](#) study, the age adjusted protocol specified different loading doses for five age groups. The first dose for each of these groups was: age up to 50 years, 10 mg; 51 to 65 years, 9 mg; 66 to 80 years, 7.5 mg; and > 80 years, 6 mg. This dose was either repeated on day two or adjusted according to INR levels. The doses were further decreased by 33% if the patients had one or more of: severe congestive failure, severe chronic obstructive airways disease, or amiodarone use. [Table 2](#) shows that by day five Roberts reported that more patients in the age adjusted group achieved a stable INR (defined as in-range on two consecutive days, or within 0.5) than the Fennerty group (48% versus 22%, $P = 0.02$), and this trend continued throughout the study ([Figure 5](#)).

Figure 5. Proportion of patients with a therapeutic INR from day of initiation (age related versus 10 mg).

Figure 5. (Continued)

In the [Gedge 2000](#) study elderly patients (≥ 65 yrs) in the age adjusted arm were given 10 mg on day one and 5 mg on day two (or less depending on INR levels). The mean time to an in-range INR was significantly longer for patients on the age adjusted regimen: age 65 to 75 years, 4.6 versus 3.8 days ($P = 0.03$); age > 75 years, 4.5 versus 3.5 days ($P = 0.003$). In both studies significantly fewer patients on the age adjusted regimens had high out-of-range INRs ([Table 2](#)).

Genotyping trials

Four studies ([Anderson 2007](#); [Burmester 2011](#); [Caraco 2008](#); [Hillman 2005](#)) (701 participants) compared loading doses that took into account patient genotype (genotype model). [Caraco 2008](#) and [Hillman 2005](#) compared 5 mg loading doses with a genetic nomogram, while [Anderson 2007](#) compared 10 mg. In the [Caraco 2008](#) study the authors used a CYP2C9 genotype-adjusted algorithm for the study group. In the [Hillman 2005](#) study the authors used rapid CYP2C9 genotyping followed by an initiation dose determined using various parameters including age, body size, co-morbidity (for example diabetes), clinical indication (for example valvuloplasty) and CYP2C9 genotype. The intervention arm of the [Anderson 2007](#) study used a rapid assay for genotyping CYP2C9 *2 and CYP2C9 *3 and VKORC1 C1173T alleles followed by a regression equation that included three genetic variants and

age, sex and weight. [Burmester 2011](#) was slightly different in that patients in both arms were loaded with warfarin based on a clinical regression algorithm model that took into account multiple clinical parameters. However, in one arm of this trial the algorithm also had additional information on the genotype of the patient. [Anderson 2007](#) and [Caraco 2008](#) reported a greater proportion of patients in-range in the genotype group on day five ([Table 2](#)). [Caraco 2008](#) also reported that the genotype groups spent significantly more time in-range ($P < 0.001$), but the figure at day five of 15% in range in the 5 mg group was significantly lower than expected at this dose in comparison to similar arms from the other 5 mg trials ([Figure 6](#)). [Anderson 2007](#) and [Hillman 2005](#) reported no significant differences between genotype guided and 5 mg or 10 mg initiation doses. In the [Burmester 2011](#) study the authors report that 61 participants (34.7%) were better predicted by the clinical only model, while 115 participants (65.3%) were better predicted by the genetic clinical model (overall $P < 0.0001$). There was no difference in the median per cent time in range within the first 14 days (28.6% in both arms, $P = 0.564$) nor in the observed median times to stable therapeutic dose (31 days, 95% CI 24 to 36 days in the clinical-only arm versus 29 days, 95% CI 23 to 36 days, $P = 0.90$). Finally, the authors reported both arms were very similar with respect to the time to INR > 4.0 ($P = 0.94$).

Figure 6. Proportion of patients with a therapeutic INR from day of initiation (genotype versus 10 mg or 5 mg).

Figure 6. (Continued)

Vitamin K given

Five studies (Ageno 2001; Caraco 2008; Crowther 1999; Harrison 1997; Hillman 2005) reported data on the administration of vitamin K (Table 2). Harrison 1997 reported administering vitamin K more frequently to patients in the 10 mg group; however, the difference was not significant and it was administered to patients with INR ≥ 4.8 . In the Crowther 1999 study only one patient in the 5 mg group was given vitamin K. In the Ageno 2001 study vitamin K was administered to more patients in the 2.5 mg group, although the difference was not significant. Two patients in the standard dosing arm of the Hillman 2005 study were administered subcutaneous vitamin K, while in the Caraco 2008 study one patient in the standard 5 mg arm was given vitamin K.

Serious adverse events

The Crowther 1999 study provided no data on adverse events. Of the remaining 10 studies, four found no adverse events in either arm of the trial (Ageno 2001; Gedge 2000; Harrison 1997; Roberts 1999). Of the remaining 5 mg versus 10 mg studies (Kovacs 2003; Quiroz 2006), the Quiroz 2006 study reported no episodes of major bleeding in the 5 mg group and one episode of major bleeding in the 10 mg group (an abdominal haematoma on day four) with an INR of 2.2 ($P > 0.5$). In the Kovacs 2003 study two episodes of major bleeding were observed, one in each group. There were three incidents of venous thromboembolism at 90 days in the 10 mg nomogram group versus none in the 5 mg nomogram group, although the authors concluded the rates of recurrence of venous thromboembolism did not differ significantly between the two groups ($P = 0.09$). Of the three studies comparing 5 mg versus 10 mg we found considerable variation in the time frames used, 5 days to 90 days, for reporting of adverse events.

In the Shine 2003 study one calculated dose patient suffered an episode of bleeding requiring transfusion while another patient in the standard dose group had a single bleeding episode requiring transfusion and contributing to the patient's death.

Of the studies that used genotyping to administer warfarin (Anderson 2007; Burmester 2011; Caraco 2008; Hillman 2005), although no significant differences were seen for adverse events no studies were adequately powered to show a difference in major bleeds. In the Hillman 2005 study five patients in the standard dosing group suffered adverse events (two episodes of epistaxis; one each of a gastrointestinal bleed, haematuria, DVT and PE). In the same study two patients in the model-based dosing suffered

adverse events (two episodes of gastrointestinal bleeding). In the Anderson 2007 study the authors reported that serious clinical events were infrequent (four episodes in the pharmacogenetic group, five in the standard group) and were unrelated to out-of-range INRs. One patient in the standard 5 mg arm of the Caraco 2008 study reported an adverse event. In the Burmester 2011 study the authors recorded all events reported to the Data Safety Monitoring Board (DSMB). These were defined as serious events that occurred during the trial including all deaths and other unanticipated health events, particularly thromboembolic events and serious haemorrhagic events. In addition, the authors decided to record all less serious thromboembolic and haemorrhagic events. Sixteen adverse events (eight in each arm) that met DSMB criteria were observed in the trial and included five deaths (three cancer, one central nervous system, and one cardiac), seven haemorrhagic and four thromboembolic events. However, the authors reported that none of the deaths were deemed to be related to the study. When calculating all thromboembolic and haemorrhagic health events identified during the trial the authors reported that a total of 100 events (six life threatening and one fatal) in 61 participants were observed in the clinical-only arm, whereas 112 events (two life threatening) in 54 participants were observed in the genetic plus clinical arm. There were insufficient data to establish whether there were any cases of warfarin-induced skin necrosis following rapid commencement. However, this may reflect the rarity of the condition (Chan 2000).

Quality of life

No data were reported on the quality of life for any of the studies.

DISCUSSION

Summary of main results

This is the first comprehensive analysis of randomised trials comparing different initiation doses of warfarin in different study populations. For comparison, we grouped the comparisons into four clinically relevant categories, 5 mg versus 10 mg (Crowther 1999; Harrison 1997; Kovacs 2003; Quiroz 2006); 5 mg versus other doses (Ageno 2001; Shine 2003); age adjusted (Gedge 2000; Roberts 1999); and genotype loading dose (Caraco 2008; Anderson 2007; Hillman 2005).

5 mg versus 10 mg loading dose

Four studies (355 participants) compared 5 mg versus 10 mg loading doses (Crowther 1999; Harrison 1997; Kovacs 2003; Quiroz

2006). Meta-analysis revealed no significant difference between the 5 mg and 10 mg doses as measured by the time to INR in-range by day five. However, two studies that used single INR measures (Harrison 1997; Kovacs 2003) found that a loading dose of 10 mg led to more patients in-range on day five, although heterogeneity was high. One of these studies (Kovacs 2003) also reported that the mean time to being in-range was significantly shorter using a 10 mg than a 5 mg loading dose. These results conflicted with the Crowther 1999 and Quiroz 2006 studies, which found that a 10 mg loading dose did not lead to more patients in-range on day five as measured by two consecutive INRs at day five. Overall, we concluded that there was no clear benefit between 5 mg versus 10 mg loading dose.

5 mg versus other doses

Two studies (322 participants) compared a 5 mg loading dose with 2.5 mg (Ageno 2001), and 5 mg with a calculated dose (Shine 2003). In the Ageno 2001 study heart valve replacement patients (INR target 1.5 to 2.6) receiving 2.5 mg took longer to achieve the therapeutic range but were less likely to have a supratherapeutic INR. The authors concluded that a lower dose (2.5 mg) was preferential in this population. Shine 2003 compared 5 mg with a calculated dose that took account of age, weight, serum albumin and active malignancy. Patients receiving the calculated dose achieved the target range quicker, although there was no difference in other end points.

Age adjusted

Two studies (192 participants) compared loading doses adjusted for age (Gedge 2000; Roberts 1999) with Fennerty's protocol or a modified Fennerty protocol in the standard arm. By day five, Roberts 1999 reported that more patients in the age adjusted group achieved a stable INR than in the Fennerty group. This was consistent with the Gedge 2000 study, which reported that the mean time to an in-range INR was significantly longer for patients on the age adjusted regimen.

In both studies significantly fewer patients on the age adjusted regimens had high out-of-range INRs.

Genotyping trials

Four studies (Anderson 2007; Burmester 2011; Caraco 2008; Hillman 2005) (701 participants) compared loading doses that took into account patient genotype (genotype model). Anderson 2007 and Caraco 2008 reported a greater proportion of patients in-range in the genotype group on day five. Caraco 2008 also reported that the genotype groups spent significantly more time in-range ($P < 0.001$), but the figure at day five of 15% in-range in the 5 mg group was significantly lower than expected at this dose in comparison to similar arms from the other 5 mg trials. The Burmester 2011 study reported that 61 participants (34.7%) were better predicted by the clinical only model, while 115 participants (65.3%) were better predicted by the genetic clinical model (overall $P < 0.0001$). However, the remaining outcomes reported by Burmester 2011 in addition to the Anderson 2007 and Hillman 2005 studies suggested no overall benefit for using genotype information.

Overall completeness and applicability of evidence

Overall, we found that a 10 mg loading dose makes a single therapeutic INR measure in-range more likely at five days. Yet when we analysed two consecutive INR measures at day five the

benefits of a 10 mg loading dose were not as apparent. The high heterogeneity between the numbers of patients in-range in the 10 mg trials at day five probably reflects that this measure is highly variable and not the best overall measure of the quality of INR control. A 5 mg loading dose compared to 2.5 mg dose slightly decreased the time to in-range by about half a day but at the expense of a greater proportion of overall higher INRs. We found some evidence that age adjusted nomograms may be of benefit in the elderly; however, trials were underpowered to detect important rates of adverse events. The evidence of benefit for genotyping proved disappointing as in the one trial which showed a significant benefit the quality of INR control for the comparator (5 mg loading dose) was substantially worse than any other 5 mg study groups in the systematic review. Recent work from a cohort of 4043 patients, which stated that the use of pharmacogenetics was appropriate for estimating the initial dose closer to the maintenance dose (Klein 2009), may have overestimated the potential usefulness of such an approach.

The question as to what is the optimal initiation dose remains unanswered by analysis of the current evidence base. A 5 mg regimen has been shown to give a more accurate prediction of maintenance dose (correlation co-efficient for predicted versus actual maintenance dose, $r = 0.985$) (Baglin 2007). Whether this gives rise to a reduction in adverse events remains unanswered. In the American College of Chest Physicians Guidelines a 5 mg loading dose is potentially appropriate in the elderly patient; in patients with impaired nutrition, liver disease or congestive heart failure; and in patients at risk of bleeding (Monagle 2012).

From our systematic review there is little evidence to support the use of genotyping, which conflicts with the US Food and Drug Administration (FDA) statement and the change in labelling for warfarin therapy, which states: "lower initiation doses should be considered for patients with certain genetic variations in CYP2C9" (Ansell 2009). Our overall findings are in accordance with an older systemic review that did not find sufficient evidence to support the use of pharmacogenetics to guide warfarin therapy (Kangelaris 2009). In addition, an editorial by Ansell 2009 notes, "most problematic is that the intervention arm of each trial is considerably different". Therefore, current use of genotyping is not underpinned by the evidence and should be discouraged.

During treatment induction with warfarin, elderly patients are especially at high risk of over-anticoagulation. Based on studies that generally show that daily maintenance doses are about 3 to 4 mg in the elderly, the evidence suggests an age adjusted initiation strategy dosage may improve the quality of control. If time is not a crucial issue then an initiation dose of 2.5 mg is a plausible alternative and the evidence suggests there is little difference between 2.5 and 5 mg doses.

A number of limitations are worth noting. Firstly, we decided in advance that we would include all adult patients commencing anticoagulation with warfarin irrespective of health condition, including atrial fibrillation (AF), DVT and PE. However, some patients with acute thrombosis may require rapid induction regimens while others, for example certain AF patients, may be suited to a slower commencement (Keeling 2011). It was not possible to delineate these populations as the majority of our included studies did not provide enough patient data to do this. Analysis of higher resolution data, for example through an individual patient database, would need to be carried out to

address this limitation, although this was beyond the scope of our review. Secondly, our conclusions are limited by the risk of bias from the included trials, which we found to be variable. Also the results are generally not significant as trials and any pooling of effects are underpowered. A large multi-centre trial is currently warranted which should address important adverse event rates by being adequately powered to detect these. Thirdly, often data were missing from the reported studies, and heterogeneity in how primary and secondary outcomes were reported meant that no firm conclusions could be drawn. This could be rectified by standardised reporting, which would include single and consecutive measures reported for outcomes at days three through to eight, follow-up for adverse events for 30 days after initiation, and proportion of INR measures > 4 . Finally, although our search was comprehensive the possibility of missing trials exists. We attempted to overcome this by citation searching and snowballing of the literature.

Quality of the evidence

Our results are not definitive because of the heterogeneity of how outcomes were reported and the size of the trials. The overall quality of the evidence was poor, particularly with the reporting of blinding of trials and allocation concealment. However, the results do raise important issues for current practice for the initiation of warfarin.

Potential biases in the review process

Although we produced a funnel plot, the small number of studies meant we were unable to exclude overall publication bias.

Agreements and disagreements with other studies or reviews

The conclusions drawn in this review are consistent with our previous review on this topic ([Heneghan 2010](#)).

AUTHORS' CONCLUSIONS

Implications for practice

Our results are not definitive as trials were generally small; however, they do raise important issues for current practice in the initiation of warfarin. There is no current evidence to suggest a 10 mg loading dose is superior to 5 mg. In the elderly, lower initiation doses or age adjusted doses may be more appropriate, leading to fewer high INRs. The question as to what is the optimal initiation dose remains unanswered by analysis of the current evidence base. There is little evidence that genotype-based initiation of warfarin is superior.

Implications for research

The review shows there is a paucity of high quality evidence to guide initiation of warfarin. Firm conclusions could not be drawn from the review because of the heterogeneity of how outcomes were reported and the size of the trials. There is a need for standardised reporting, which would include single and consecutive measures reported for outcomes at days three through to eight, follow-up for adverse events for 30 days after initiation, and the proportion of INR measures > 4 . Furthermore, an adequately powered multi-centre trial is warranted to assess important adverse events.

ACKNOWLEDGEMENTS

The University Department of Primary Health Care is part of the National Institute of Health Research School of Primary Care Research, which provides financial support for senior investigators who contributed to this article. Kamal R Mahtani is a holder of a National Institute of Health Research Academic Clinical Lectureship in General Practice.

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van Walraven C, Hart RG, Connolly S, Austin PC, Mant J, Hobbs FD, et al. Effect of age on stroke prevention therapy in patients with atrial fibrillation: the atrial fibrillation investigators. *Stroke* 2009;**1940**:1410-6.

Wadelius 2009

Wadelius M, Chen LY, Lindh JD, Eriksson N, Ghorji MJ, Bumpstead S, et al. The largest prospective warfarin-treated cohort supports genetic forecasting. *Blood* 2009;**113**:784-92.

Wan 2008

Wan Y, Heneghan C, Perera R, Roberts N, Hollowell J, Glasziou P, et al. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. *Circulation. Cardiovascular Quality and Outcomes* 2008;**1**(2):84-91.

Whitlock 2012

Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH. Antithrombotic and thrombolytic therapy for valvular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;**141**(2 Suppl):e576S-600S. [1931-3543: (Electronic)]

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ageno 2001

Study characteristics

Methods	Randomised controlled trial
Participants	<p>Hospital inpatients in Canada and Italy commencing warfarin after heart valve replacement.</p> <p>Enrollment: 5 mg group - 123, 2.5 mg group - 122 - 48 excluded. Analysis of: 113 in 5 mg group and 84 in 2.5 mg group.</p> <p>5 mg group: 56% male, Av age 65.2, BMI 26.2, amiodarone 11%.</p> <p>2.5 mg group: 56.6% male, Av age 64.2, BMI 28.7, amiodarone 11%.</p> <p>Inclusion: Hospital inpatients after heart valve replacement with INR target 1.5-2.6.</p> <p>Exclusion: Patients with INR > 1.3 on day 0.</p>
Interventions	Warfarin: 5 mg for 2 days, then adjusted if necessary versus 2.5 mg fixed dose adjusted if < 1.5 or >3.0 from day 3.
Outcomes	Proportion of INR > 2.6, time to therapeutic range, daily mean INR values, INR < 1.5 on day 3, INR > 3.0 on day 3, vit K given, number of reduced doses, number of withheld doses, bleeding, thrombotic events.
Notes	48 excluded: 13 enrolled in error, 35 - most of whom were randomised to 2.5 mg - received a dose which differed from the protocol.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer generated random number table
Allocation concealment (selection bias)	Unclear risk	No allocation concealment mentioned
Blinding (performance bias and detection bias) All outcomes	High risk	More patients in the 2.5 mg group received a dose which differed from protocol. Study authors postulated that staff responsible for dosing had an initial "distrust" of the protocol
Incomplete outcome data (attrition bias) All outcomes	High risk	Patients who received a dose which differed from the protocol were excluded from analysis
Selective reporting (reporting bias)	Low risk	Relevant outcomes assessed and reported for both groups
Other bias	High risk	35 patients - most of whom were randomised to 2.5 mg - received a dose which differed from the protocol

Anderson 2007

Study characteristics

Methods	Randomised controlled trial
Participants	<p>USA study. Largely hospital inpatients being initiated on warfarin.</p> <p>Enrollment: 206 patients - 5 excluded. Analysis of pharmacogenetic group (PG) - 101 versus standard group (STD) - 99.</p> <p>PG group: 49.5% male, Mn age 63.2, Weight 92.1 kg.</p> <p>STD group: 56.6% male, Mn age 58.9, Weight 94.7 kg</p> <p>Inclusion: ≥ 18 yrs, target INR 2 - 3.</p> <p>Exclusion: < 18 yrs, pregnant women, lactating or of child-bearing potential; other investigational trials within 30 days, rifampin within 3 wks, co-morbidities which precluded standard dosing (e.g. advanced age, renal insufficiency, hepatic insufficiency, terminal disease).</p>
Interventions	Warfarin: twice dose estimated by genotype for 2 days (PG) versus 10 mg for 2 days (standard group - Std).
Outcomes	Proportion of INR < 1.8 or > 3.2 , time to supra therapeutic INR, proportion of time within therapeutic range, within therapeutic range on day 5, within therapeutic range on day 8, serious adverse events, INR ≥ 4 , subtherapeutic INR on day 4, number of measurements, number of dose adjustments.
Notes	<p>206 patients randomised - 5 enrolled in error, 1 self-withdrawal.</p> <p>Diagnostic criteria: PG group: orthopaedic 65.3%, VTE 18.8%, AF 12.9%; STD group orthopaedic 54.5%, VTE 28.3%, AF 15.2%.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permutated blocks of 5
Allocation concealment (selection bias)	Unclear risk	No allocation concealment mentioned
Blinding (performance bias and detection bias) All outcomes	Low risk	Assignment was blinded to patients and to clinicians/investigators and known only to a research assistant and the pharmacist
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis on 200 patients
Selective reporting (reporting bias)	Low risk	Relevant outcomes assessed and reported for both groups
Other bias	High risk	Imbalance between groups - older age and more hypertension in pharmacogenetic group (PG)

Burmester 2011

Study characteristics

Methods	Randomised controlled trial
Participants	<p>USA study. Largely private hospital inpatients being initiated or restarted on warfarin.</p> <p>Enrollment: 230 patients – 46 withdrew/failed to fully complete trial. Analysis of genotype + clinical information algorithm group (Gen + Clin) - 115 versus clinical info algorithm only group (Clin) - 115.</p> <p>Gen + Clin group: 56% male, Mn age 67.4 years, body surface area (BSA) 1.96.</p> <p>Clin group: 51% male, Mn age 69.2, BSA 1.98</p> <p>Inclusion: ≥ 40yrs, target INR 2 - 3.5, white ethnicity, effective method of contraception in women of childbearing potential.</p> <p>Exclusion: < 40 yrs, pregnancy, known Native American, African American or Asian descent, thrombocytopenia, severe to moderate hepatic insufficiency, other clinical contraindications as deemed by patient's physician.</p>
Interventions	Warfarin: estimated by genotype and clinical parameters (male gender, valve replacement, age and BSA) for 60 days (Gen + Clin) versus clinical parameters only for 60 days (Clin).
Outcomes	Absolute prediction error relative to therapeutic dose, time within therapeutic target range during first 14 days, time to therapeutic dose, time to first INR > 4, warfarin related adverse events.
Notes	<p>230 patients randomised – 18 and 28 discontinued early from Gen + Clin and Clin groups respectively. Data used in analysis differed for group and outcomes; Gen + Clin prediction error outcome n = 91, time in range outcome n = 113. Clin n = 85 and 112 respectively.</p> <p>Trial was closed with less (15) patients in each arm than anticipated (130) due to slow recruitment rate. Power to detect significant differences in time to therapeutic range outcome was subsequently very low.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly alternating block sizes of 2 and 4
Allocation concealment (selection bias)	Unclear risk	No allocation concealment mentioned
Blinding (performance bias and detection bias) All outcomes	Low risk	Genotype was blinded to patients, nurses and physicians but unsure if laboratory staff/investigators were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Primary outcome data available for 98% subjects for time in range but only 77% for prediction error assessment
Selective reporting (reporting bias)	Low risk	Relevant outcomes assessed and reported for both groups
Other bias	Unclear risk	Imbalance in drop-outs between groups – 25% versus 15%, Clin versus Gen + Clin

Caraco 2008

Study characteristics

Methods	Randomised controlled trial
Participants	<p>Israeli study of patients in university hospital.</p> <p>Enrollment: 283 - warfarin not initiated in 31. Study group 126 - 31 excluded; Control group 126 - 30 excluded.</p> <p>Study group 95; Control group 96.</p> <p>Study group: Age 57.6 ± 19.6, % Male 48%, Weight 82.4 ± 17.7.</p> <p>Control group: Age 59.7 ± 18.5, % Male 44%, Weight 78.3 ± 16.5.</p> <p>Inclusion: warfarin naive patients diagnosed with AFIB, DVT or PE, scheduled to receive warfarin.</p> <p>Exclusion: < 18yrs and baseline INR > 1.4.</p>
Interventions	<p>Warfarin: genotype-adjusted algorithm versus 5 mg on day 1, and then adjusted as necessary.</p> <p>Patients co-administered with amiodarone, antibiotics, anticonvulsants, some "statins" had their algorithms reduced by an average of 25%.</p>
Outcomes	Time to INR in range, time to stable anticoagulation, Time in range, days outside therapeutic range, bleeding, thromboembolic events, sum of deviations from desired range.
Notes	Study was in 2 parts covering initiation and also maintenance of warfarin dose.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Allocated on basis of whether last digit of patient ID was an odd or even number
Allocation concealment (selection bias)	Unclear risk	No allocation concealment mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Investigators were not involved in the recruitment/randomisation or genetic analysis
Incomplete outcome data (attrition bias) All outcomes	High risk	283 randomised - 92 excluded
Selective reporting (reporting bias)	Low risk	Relevant outcomes assessed and reported for both groups
Other bias	Unclear risk	Demographic differences at baseline - higher rate of hyperlipidaemia, more DVT/PE in control group. INR levels in 5mg group lower than reported in other studies

Crowther 1999

Study characteristics

Methods	Randomised controlled trial
Participants	<p>Canadian study. Patients being initiated on warfarin at a thromboembolism unit.</p> <p>53 patients enrolled: 1 patient excluded from 5 mg group. Analysis of: 5 mg group - 31 versus 10 mg group - 21.</p> <p>5mg group: Mn age 65.5 years, Mn weight 82 kg.</p> <p>10mg group: Mn age 66.7, Mn weight 78.3 kg.</p> <p>Inclusion: patients being initiated on warfarin with an INR target 2 - 3.</p> <p>Exclusion: contraindication to warfarin or geographically inaccessible.</p>
Interventions	warfarin: 10 mg versus 5 mg on days 1 and 2, adjusted as necessary thereafter.
Outcomes	INR 2 - 3 on 2 consecutive days, INR > 3 on day 4.
Notes	1 patient in 5 mg group received vit K on day 2 of the study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random numbers table
Allocation concealment (selection bias)	Unclear risk	No allocation concealment mentioned
Blinding (performance bias and detection bias) All outcomes	High risk	Patients advised of dose, nursing staff and physicians aware
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5 patients did not complete the required blood testing and worst case scenario modelling used to test for any difference in significance. 1 patient from 5 mg group excluded from the analysis.
Selective reporting (reporting bias)	Low risk	Relevant outcomes assessed and reported for both groups.
Other bias	Unclear risk	<p>1 patient in 5 mg group excluded from analysis. 47% male in study but gender balance between groups not reported.</p> <p>Difference in size of groups due to an underlying imbalance in random numbers table.</p>

Gedge 2000

Study characteristics

Methods	Randomised trial
Participants	UK hospital inpatients.

Gedge 2000 (Continued)

127 patients randomised - 7 patients excluded. 120 patients included in the analysis.

4 groups of 30 patients - Aged 65 - 75 yrs and > 75yrs/New induction and Fennerty.

New induction 65 - 75yrs: Mn Age 70.3; % Male 57.

Fennerty 65 - 75yrs: Mn Age 70.5, % Male 43.

New induction > 75 yrs Mn Age 80.5, % Male 40.

Fennerty > 75 yrs Mn Age 80.3, % Male 60.

Interventions	New induction: 10 mg on day 1 and 5 mg on day 2 if INR < 1.8 versus Fennerty 10 mg on day 1 and 10 mg on day 2 if INR < 1.8.
Outcomes	INR > 4.5, bleeding, vit K given, doses omitted, time within therapeutic range, maintenance dose predicted on day 4.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned in paper
Allocation concealment (selection bias)	Unclear risk	Not mentioned in paper
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned in paper
Incomplete outcome data (attrition bias) All outcomes	High risk	7 patients withdrawn: 6 because of prescribing failures (3 per regimen) and 1 because INR not checked on day 4
Selective reporting (reporting bias)	Low risk	Relevant outcomes assessed and reported for both groups
Other bias	Unclear risk	7 patients withdrawn: 6 because of prescribing failures (3 per regimen) and 1 because INR not checked on day 4 Differences in gender balance between groups

Harrison 1997

Study characteristics

Methods	Randomised using a random number table
Participants	Canadian inpatients and outpatients with venous thromboembolism and other conditions. 51 patients were enrolled - 2 excluded (1 died, one required cardiac catheterization). 5 mg - 24 patients; 10 mg - 25 patients. Mean age 66.2/63.4 years.

Harrison 1997 (Continued)

Inclusion criteria: Patient requiring anticoagulation with a target INR of 2.0 to 3.0.

Interventions	Warfarin: 5 mg for 2days versus 10 mg for 2 days on initiation of warfarin
Outcomes	Time to INR in range, INR > 3.0, vit K given, serious adverse event.
Notes	Published as a short communication. Additional information was published in authors responses to letters.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described
Blinding (performance bias and detection bias) All outcomes	High risk	Patients and health care professionals were not blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	High risk	Two patients excluded. By 108 hours, INR values missing for 7 patients in 5 mg group and 8 patients in 10 mg group
Selective reporting (reporting bias)	Low risk	Relevant outcomes assessed and reported for both groups
Other bias	Unclear risk	2 excluded after (unmentioned) initial dose - one died and one required cardiac catheterization

Hillman 2005
Study characteristics

Methods	Prospective, randomised single-blinded clinical pilot trial
Participants	43 patients eligible - 5 declined to participate. 5 mg dose: 20; model-based dose: 18. Inclusion: eligibility for warfarin therapy based on diagnosis. Exclusion: Antiphospholipid antibodies, contraindications for warfarin, previous exposure to warfarin, liver disease, renal disease, non-Caucasian race, < 40yrs.
Interventions	Warfarin: 5 mg daily for 28 days versus dose assessed from multivariate model and CYP2C9 genotype.
Outcomes	Primary outcome was feasibility of a trial. Other outcomes reported: percentage time INR in-range, percentage INR > 4.
Notes	Patients recruited from:vascular laboratory, electrocardiography laboratory, department of orthopedics, department of cardiology, outpatient and inpatient pharmacies.

Hillman 2005 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random table
Allocation concealment (selection bias)	Low risk	Patient data entered on recruitment into a database which contained a concealed randomisation table
Blinding (performance bias and detection bias) All outcomes	High risk	Doses communicated to attending physician. Patient unaware "single-blind" by definition
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were followed on protocol after initiation of therapy
Selective reporting (reporting bias)	Low risk	Relevant outcomes assessed and reported for both groups
Other bias	Unclear risk	Frequent INR determinations not being obtained on study patients discharged to nursing homes. Imbalance in groups for clinical indications - more atrial fibrillation/flutter patients in 5mg group and more DVT/PE patients in model based group

Kovacs 2003

Study characteristics

Methods	Randomised controlled clinical trial
Participants	<p>Canadian thromboembolism outpatient services of tertiary care hospital.</p> <p>201 of 210 consecutive patients.</p> <p>5 mg group: 97 10 mg group: 104.</p> <p>5 mg: Mn Age 55.6 ± 17.2 years; % Male 48%; MnWeight (kg) 83.4 ± 20.</p> <p>10 mg: Mn Age 55.4 ± 17.4; % Male 63%; Mn Weight (kg s) 83.5 ± 18.6.</p> <p>Inclusion: patients with a diagnosis of objectively confirmed acute venous thromboembolism.</p> <p>Exclusion: INR > 1.4, thrombocytopenia, < 18years, required hospitalisation, anticoagulation therapy in previous 2 weeks, high risk for major bleeding.</p>
Interventions	Warfarin: 5 mg for 2 days versus 10 mg for 2 days. Adjusted as necessary from day 3.
Outcomes	Time to INR > 1.9, proportion of patients with INR 2 - 3 on day 5, recurrent thromboembolism within 90 days, major bleeding within 28 days, number of INR > 5, number of INR assessments in 28 days, 90 day survival.
Notes	An adjudication committee evaluated all clinical events in a blinded fashion.

Risk of bias

Kovacs 2003 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomisation
Allocation concealment (selection bias)	Low risk	Allocation was not known by investigators and was contained in opaque sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind (physician-patient)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all patients
Selective reporting (reporting bias)	Unclear risk	Time to stable INR - i.e. 2 days not reported, results report patients therapeutic by day 5 though outcome described as on day 5. Supratherapeutic INR reported for 4 weeks. Serious adverse events over 90 days
Other bias	Low risk	

Quiroz 2006
Study characteristics

Methods	Randomised trial
Participants	372 patients screened for eligibility, 322 excluded. 10 mg group: 25, 5 mg group 25. Inclusion: DVT confirmed by venous ultrasound or PE confirmed by chest computed tomography. Exclusion: received treatment with heparin or warfarin for > 36hours, had life expectancies of < 3mths, unable to participate in 2 week follow-up visits, < 18yrs, estimated creatinine clearances of < 30ml/min, contraindications to anticoagulation or high risk of major bleeding.
Interventions	Warfarin: 5 mg for 2 days vs 10 mgs for 2 days. Adjusted as necessary from day 3. INR tested on days 1, 2, 3, 4, 5, 6, 7, 10 and 14.
Outcomes	Number of days to 2 consecutive INRs > 1.9, recurrent venous thromboembolism, death, major bleeding, INR > 5.
Notes	Patients with acute VTE only.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	1:1 computer generated allocation
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described

Quiroz 2006 (Continued)

Blinding (performance bias and detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	All comparisons were made on an intention-to-treat basis
Selective reporting (reporting bias)	Low risk	Relevant outcomes assessed and reported for both groups
Other bias	Low risk	

Roberts 1999

Study characteristics

Methods	Randomised trial
Participants	<p>Patients commencing warfarin at 2 teaching hospitals.</p> <p>3 groups: Age 37; Fenn 30; Emp 123 (data collected retrospectively & used as basis for Age protocol - not included in this analysis).</p> <p>Age Group: Weight 77 ± 16, % Male 66%.</p> <p>Fenn Group: Weight 79 ± 12, % Male 75%.</p> <p>Inclusion: Patients with a target INR 2 - 3.</p> <p>Exclusion: Patients undergoing MVR or AVR (target INR 2.5 - 3.5).</p> <p>2 excluded from Age group - advanced malignancy and mistaken classification; 2 excluded from the Fenn group - wrong dose given, co-incidental bleeding (INR < 2).</p>
Interventions	Age - initial dose depending on age category day 1, then adjusted if necessary versus Fenn.
Outcomes	Time taken to stable therapeutic INR, proportion with INR ≤ 4 , dose held.
Notes	Patients had doses reduced by 33% if they had severe CCF, severe COAD or amiodarone use.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Surgical units were assigned to use the Age protocol for the first 6 weeks and the Fenn protocol for the remaining 6 weeks
Allocation concealment (selection bias)	High risk	Assignment of warfarin regimen was by the treating medical unit. Eight medical units were assigned to use either the Age or Fenn protocols
Blinding (performance bias and detection bias) All outcomes	High risk	Patients and health care professionals were not blinded
Incomplete outcome data (attrition bias)	High risk	Patients excluded from the groups were not included in the analysis

Roberts 1999 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	Relevant outcomes assessed and reported for both groups
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Shine 2003
Study characteristics

Methods	Randomised trial
Participants	100 patients. 46 standard dose; 44 calculated dose. Inclusion: anticoagulation to INR 2 - 3, INR prior to enrollment 1.4, warfarin not prescribed in previous 3 months.
Interventions	5 mg (standard dose) versus calculated dose.
Outcomes	Days to anticoagulation, complications, activity of factor II and protein C.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved by assigning to 200 study packets both an ordinal and random number. Patients were assigned to next packet ordinal number and treated with 5mg if the random number was greater than the median for all random numbers
Allocation concealment (selection bias)	High risk	Patients were assigned to next packet ordinal number and treated with 5 mg if the random number was greater than the median for all random numbers
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Separate analysis on 61 completers and 39 non-completers
Selective reporting (reporting bias)	Low risk	Relevant outcomes assessed and reported for both groups
Other bias	Unclear risk	Separate analysis on 61 completers and 39 non-completers

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Doecke 1991	Study compared warfarin dosing by nomogram with dosing by resident medical staff. Empirical dosing varied according to the judgement of the professional prescribing.
Hameed 2008	Study compared uniform versus non-uniform warfarin dosages. This was a cross-over study using healthy subjects.
Iguchi 1994	Study compared 6 mg for 3 days versus 16 mg for 2 or 3 days. However outcomes were Protein C and Factor X response and changes in INR during warfarin treatment which were not comparable.
Kovacs 1999	Study compared warfarin dosing by nomogram with dosing by attending physician. Attending physicians varied dose according to individual judgement.
Schulman 1984	Study compared a "low-dose" with a "high-dose" warfarin loading dose regimen. Outcome was number of days to stable therapeutic PT-level. However stable therapeutic PT was defined as INR 2.2 - 4.5 and was not comparable.
Van Den 2002	Study compared the dosing of acenocoumarol in orthopaedic and surgical patients using an algorithm with routine dosing.
van Schie 2011	Study compared loading and maintenance dose algorithms for phenprocoumon and acenocoumarol.

DATA AND ANALYSES

Comparison 1. 5 mg versus 10 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 INR in-range by day 5: 5mg v 10mg	4	352	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.77, 1.77]
1.2 Single INR measure	2	250	Risk Ratio (M-H, Random, 95% CI)	1.49 [1.01, 2.21]
1.3 Consecutive INR measures	2	102	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.62, 1.19]

Analysis 1.1. Comparison 1: 5 mg versus 10 mg, Outcome 1: INR in-range by day 5: 5mg v 10mg

Analysis 1.2. Comparison 1: 5 mg versus 10 mg, Outcome 2: Single INR measure

Analysis 1.3. Comparison 1: 5 mg versus 10 mg, Outcome 3: Consecutive INR measures

ADDITIONAL TABLES

Table 1. Dosing regimes

Study	Dosing Protocol on Days 1 and 2 (Reference for nomogram used)
10 mg trials	
Harrison 1997 ξ	5 mg on day 1, up-to 5 mg on day 2 versus 10 mg on day 1, up-to 10 mg on day 2

Table 1. Dosing regimes (Continued)

Crowther 1999	5 mg on day 1, up-to 5 mg on day 2 versus 10 mg on day 1, up-to 10 mg on day 2
ξ	
Kovacs 2003	5 mg versus 10 mg on days 1 and 2
δ	
Quiroz 2006	5 mg versus 10 mg on days 1 and 2
5 mg trials	
Ageno 2001	5 mg day 0 (subsequent doses adjusted) versus 2.5 mg on days 0 through 4 (dose modified if < 1.5 or > 3.0 on day 3)
Shine 2003	5 mg on day 1, up-to 5 mg on day 2 versus calculated dose on day 1, up-to 100% calculated dose on day 2
Age trials	
Roberts 1999	Age adjusted nomogram (6 - 10 mg) on day 1, 0.5 - 10 mg on day 2 versus Fennerty protocol (10 mg on day 1, 0.5 mg - 10 mg on day 2)
ψ	
Gedge 2000	Age stratified 65 - 75 years & 75 yrs - 10 mg on day 1, up to 5 mg on day 2 versus Modified Fennerty protocol, 10 mg day 1 and up to 10 mg on day 2
Genotyping trials	
Hillman 2005	5 mg on days 1 and 2 versus Model - genetic nomogram
Anderson 2007	10 mg on days 1 and 2 versus Model - 2 × predicted maintenance dose on days 1 and 2 followed by predicted dose
Caraco 2008	5 mg on day 1 and up-to 5 mg on day 2 versus Model - genetic nomogram
Burmester 2011	Warfarin dosing based on an algorithm using relevant genetic polymorphisms and clinical parameters (genetic clinical arm) versus an algorithm using only usual clinical parameters (clinical only arm)

ξ Crowther 1997 report: Crowther MA, Harrison L, Hirsh J. [Adelman 1997](#) Reply: Warfarin: Less May Be Better. Annals of Internal Medicine 1997 August 15;127(4):333.

δ [Kovacs 2002](#) MJ, Anderson DA, Wells PS. Prospective assessment of a nomogram for the initiation of oral anticoagulation therapy for outpatient treatment of venous thromboembolism. Pathophysiology of Haemostasis and Thrombosis 2002;321:131-3.

ψ [Fennerty 1984](#) et al. Flexible induction dose regimen for warfarin and prediction of maintenance dose. British Medical Journal Clinical Research Ed 1984 April 28;288(6426):1268-70.

Table 2. Summary of primary outcome results (time to stable INR, supratherapeutic INR, subtherapeutic INRs, vitamin K given, and serious adverse events)

		Pro- portion in INR range							
Study	Dosing	Day 3 (95% CI)	Day 5 (95% CI)	Mean time to time in range Days (SD)	INR ≥4 unless other- wise stated %	Vit K Given N (%)	Serious Adverse Events N (%)	Other primary endpoints	
5 mg v 10 mg									
Harrison 1997	5 mg	42%	67% [§]	-	-	1(4%)	0		
	10mg	36%	80% [§]	-	-	4(16%)	0		
Crowther 1999	5 mg	50% (26 to 75)	88% (75 to 102)			1(3%)	-	INR 2.0 - 3.0 for 2 consecutive days and not > 3.0	P < .003
	10 mg	33% (-2 to 68)	69% (39 to 99)	-	-	0	-	10 mg (24%) v 5 mg (66%) RR 2.22 (95% CI 1.3 - 3.7)	
Kovacs 2003	5 mg	3%*	46% (36 to 57)** P<0.001	5.6 (1.4)	INR ≥ 5 11%	-	2 (2%)		
	10 mg	25%*	83% (74 to 89)**	4.2 (1.1)	9%	-	4 (4%)		
Quiroz 2006	5 mg	-	52%**	Median 5	INR > 5 0%	-	0		
	10 mg	-	56%**	Median 5	0%	-	1 (4%)		
5mg v other doses									

Table 2. Summary of primary outcome results (time to stable INR, supratherapeutic INR, subtherapeutic INRs, vitamin K given, and serious adverse events) (Continued)

Ageno 2001	5 mg		2.0 (1.0)	P < .0001		3(3%)	0	INR > 2.6 5 mg (42%)		P < .05
	2.5 mg		2.7 (1.2)	P < .0001		5(6%)	0	2.5 mg (26%)		P < .05
Shine 2003	Std (5 mg)	63%†	5 (0.9)¥	P = .007	"high" INR 2%	-	1(2%)			
	Calc	77%†	4.2 (0.9)¥	P = .007	INR > 4.4 5%	-	1(2%)			
Age tri-als										
Roberts 1999	Age ad-justed	47%*	3.7 (1.3)Φ		6%	-	0	INR 2.0 - 3.0 for 2 consecutive days		
	Fennerty	25%*	4.3 (1.2)Φ		32%	-	0	Age v Fennerty		P = .003
INR >4.5										
Mean days in range (SD)										
Gedge 2000	Age 65 - 75 yrs	-	4.6 (1.6)	P = .03	3% P < .05	0	0	Age	3.0 (1.3)	P = .003
	New Fen-nerty 65-75 yrs	-	3.8 (0.8)	P = .03	20% P < .05	^	0	New Fennerty	2.7 (1.3)	P = .003
INR > 4.5										
Mean days in range (SD)										
	Age > 75 yrs		4.5 (1.4)	P = .003	3% P < .01	0	0	Age	2.9 (1.1)	P = .04
	New Fen-nerty >75 yrs	-	3.5 (0.7)	P = .003	37% P < .01	^	0	New Fennerty	2.4 (1.3)	P = .04
Geno-typing										

Table 2. Summary of primary outcome results (time to stable INR, supratherapeutic INR, subtherapeutic INRs, vitamin K given, and serious adverse events) (Continued)

Hillman 2005	Model					33%	0	2 (10%)	% time INR in range	
									5 mg 42%	
	5 mg					30%	2 (doses)	5 (28%)	Model 42%	
Ander- son 2007	Model					30%	-	4 (4%)	average % of INR outside range	
									10 mg 33%	
	5 mg					37%	-	5 (%)	Model 31%	
									% time in INR range	
Caraco 2008	Model	1%*	49%*	4.8 (1.5)	P < .001	-	0	0	5 mg 25%	P < .001
	STD 5 mg	1%*	11%*	7.5 (3.1)	P < .001	-	1 (1%)	1 (1%)	Model 45%	P < .001
Burmester 2011	Clinical parame- ters only	-	-	-		35% ^α	-	8 events	Prediction error relative to therapeutic dose: 61 subjects (34.7%) were better predicted by the clinical only model Time in therapeutic target range ^λ	
	Clinical and genet- ic parame- ters	-	-	-		38% ^α	-	8 events ^β	Prediction error relative to therapeutic dose: 115 subjects (65.3%) were better predicted by the genetic clinical model. Time in therapeutic target range ^λ	

- * taken from the published graph
- § includes discharged with INR in-range from (Ann int Med vol 127, 4, pg 133)
- ** in-range by day 5
- † INR within range on or before day 6
- ¥ completers only
- Φ author correspondence
- ^ 1 (age not stated)
- α $P = 0.94$
- β according to Data Safety Monitoring Board (DSMB) criteria. Additional events whether or not they met the DSMB criteria for review, were also summarized in the article
- λ The medians for the simple percent time in range were 28.6% in both arms ($P = 0.564$)

APPENDICES

Appendix 1. Search strategies

The Cochrane Library (CENTRAL and DARE)

```
#1 MeSH descriptor Anticoagulants, this term only
#2 MeSH descriptor Warfarin explode all trees
#3 warfarin*
#4 anticoagula*
#5 anti-coagula*
#6 coumadin*
#7 warfant*
#8 marevan*
#9 aldocumar*
#10 tedicumar*
#11 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
#12 ((fennerty* or age adjusted or empirical or fixed) near5 (regime* or method* or protocol* or algor?thm*))
#13 MeSH descriptor Nomograms explode all trees
#14 ((initial or initiation or induction or loading or start*) near5 (method* or protocol* or algor?thm* or regime* or nomogram*))
#15 ((dose* or dosage* or dosing) near5 (empirical or regime* or method* or protocol* or algor?thm* or nomogram*))
#16 ((initial or initiation or induction or loading or start*) near3 (dose* or dosage* or dosing))
#17 (#12 OR #13 OR #14 OR #15 OR #16)
#18 (#11 AND #17)
```

Ovid MEDLINE (1950 on)

```
1 Anticoagulants/
2 Warfarin/
3 anticoagula*.ti.
4 coumadin*.ti.
5 warfarin*.ti.
6 or/1-5
7 ((initial or initiation or induction or loading or start*) adj3 (dose* or dosage* or dosing)).tw.
8 ((fennerty* or age adjusted or empirical or fixed) adj5 (regime* or method* or protocol* or algor#thm*)).tw.
9 Nomograms/
10 ((initial or initiation or induction or loading or start*) adj3 (method* or protocol* or algor#thm* or regime* or nomogram*)).tw.
11 ((dose* or dosage* or dosing) adj5 (empirical or regime* or method* or protocol* or algor#thm* or nomogram*)).tw.
12 or/7-11
13 randomised controlled trial.pt.
14 controlled clinical trial.pt.
15 randomized.ab.
16 placebo.ab.
17 drug therapy.fs.
18 randomly.ab.
19 trial.ab.
20 groups.ab.
21 or/13-20
22 exp animals/ not humans.sh.
23 21 not 22
24 6 and 12 and 23
```

Ovid EMBASE (1980 on)

```
1 anticoagulant agent/
2 Warfarin/
3 anticoagula*.ti.
4 anti-coagula*.ti.
5 coumadin*.ti.
6 warfarin*.ti.
7 or/1-6
8 ((initial or initiation or induction or loading or start*) adj3 (dose* or dosage* or dosing)).tw.
9 loading drug dose/
```

10 ((fennerty* or age adjusted or empirical or fixed) adj5 (regime* or method* or protocol* or algor#thm*)).tw.
 11 nomogram/
 12 ((initial or initiation or induction or loading or start*) adj3 (method* or protocol* or algor#thm* or regime* or nomogram*)).tw.
 13 ((dose* or dosage* or dosing) adj5 (empirical or regime* or method* or protocol* or algor#thm* or nomogram*)).tw.
 14 or/8-13
 15 random\$.tw.
 16 factorial\$.tw.
 17 crossover\$.tw.
 18 cross over\$.tw.
 19 cross-over\$.tw.
 20 placebo\$.tw.
 21 (doubl\$ adj blind\$).tw.
 22 (singl\$ adj blind\$).tw.
 23 assign\$.tw.
 24 allocat\$.tw.
 25 volunteer\$.tw.
 26 crossover procedure/
 27 double blind procedure/
 28 randomised controlled trial/
 29 single blind procedure/
 30 or/15-29
 31 (animal/ or nonhuman/) not human/
 32 30 not 31
 33 7 and 14 and 32

WHAT'S NEW

Date	Event	Description
21 September 2021	Review declared as stable	The topic is of low priority for the current portfolio of the Heart Group.

HISTORY

Protocol first published: Issue 9, 2010

Review first published: Issue 12, 2012

CONTRIBUTIONS OF AUTHORS

Kamal R Mahtani (KM) wrote the first draft of this review with contributions from Carl Heneghan (CH), David Nunan (DN), Clare Bankhead (CB) and Sian Harrison (SH). Further advice and contributions were given by Richard Hobbs (RH), Rafael Perera (RP) and Alison Ward (AW).

DECLARATIONS OF INTEREST

The authors declare that there are no competing interests.

SOURCES OF SUPPORT

Internal sources

- New Source of support, Other

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Rafael Perera's work on this review has been partially funded by an NIHR HTA grant on Monitoring Long term Conditions

INDEX TERMS

Medical Subject Headings (MeSH)

Age Factors; Anticoagulants [*administration & dosage] [adverse effects]; International Normalized Ratio; Randomized Controlled Trials as Topic; Warfarin [*administration & dosage] [adverse effects]

MeSH check words

Humans