Genotype-guided versus standard vitamin K antagonist dosing algorithms in patients initiating anticoagulation

A systematic review and meta-analysis

Emilie P. Belley-Cote[1]; Hasib Hanif[2]; Frederick D'Aragon[1,3]; John W. Eikelboom[4,5]; Jeffrey L. Anderson[6]; Mark Borgman[7]; Daniel E. Jonas[8]; Stephen E. Kimmel[9]; Vangelis G. Manolopoulos[10]; Ekaterina Baranova[11]; Anke H. Maitland-van der Zee[11]; Munir Pirmohamed[12]; Richard P. Whitlock[1,2,5]

[1]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada; [2]Division of Cardiac Surgery, McMaster University, Hamilton, Ontario, Canada; [3]Anaesthesiology Department, Sherbrooke University, Quebec, Canada; [4]Department of Medicine, McMaster University, Hamilton, Ontario, Canada; [5]Population Health Research Institute, Hamilton, Ontario, Canada; [6]Intermountain Medical Center, Murray, Utah, USA; [7]PGXL Labs, Louisville, Kentucky, USA; [8]University of North Carolina Chapel Hill, Chapel Hill, North Carolina, USA; [9]University of Pennsylvania, Philadelphia, Pennsylvania, USA; [10]Laboratory of Pharmacology, Democritus University of Thrace Medical School, Alexandroupolis, Greece; [11]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands; [12]University of Liverpool, Liverpool, UK

Summary

Variability in vitamin K antagonist (VKA) dosing is partially explained by genetic polymorphisms. We performed a meta-analysis to determine whether genotype-guided VKA dosing algorithms decrease a composite of death, thromboembolic events and major bleeding (primary outcome) and improve time in therapeutic range (TTR). We searched MEDLINE, EMBASE, CENTRAL, trial registries and conference proceedings for randomised trials comparing genotype-guided and standard (non genotype-guided) VKA dosing algorithms in adults initiating anticoagulation. Data were pooled using a random effects model. Of the 12 included studies (3,217 patients), six reported all components of the primary outcome of mortality, thromboembolic events and major bleeding (2,223 patients, 87 events). Our meta-analysis found no significant difference between groups for the primary outcome (relative risk 0.85, 95 % confidence interval [CI] 0.54–1.34; heterogeneity X^2=4.46, p=0.35, I^2=10 %). Based on 10 studies (2,767 patients), TTR was significantly higher in the genotype-guided group (mean difference (MD) 4.31 %; 95 % CI 0.35, 8.26; heterogeneity X^2=43.31, p< 0.001, I^2=79 %). Pre-specified exploratory analyses demonstrated that TTR was significantly higher when genotype-guided dosing was compared with fixed VKA dosing (6 trials, 997 patients: MD 8.41 %; 95 % CI 3.50,13.31; heterogeneity X^2=15.18, p=0.01, I^2=67 %) but not when compared with clinical algorithm-guided dosing (4 trials, 1,770 patients: MD –0.29 %; 95 % CI –2.48,1.90; heterogeneity X^2=1.53, p=0.68, I^2=0 %; p for interaction=0.002). In conclusion, genotype-guided compared with standard VKA dosing algorithms were not found to decrease a composite of death, thromboembolism and major bleeding, but did result in improved TTR. An improvement in TTR was observed in comparison with fixed VKA dosing algorithms, but not with clinical algorithms.

Keywords

Anticoagulants, genetics, meta-analysis, pharmacogenomics, warfarin

Correspondence to:
Richard Whitlock
David Braley Cardiac, Vascular and Stroke Research Institute
Room 1C1–5B, 237 Barton St. E.
Hamilton, Ontario L8L 2X2, Canada
Tel.: +1 905 527 4322 ext. 44091, Fax: +1 905 577 8017
E-mail: Richard.Whitlock@phri.ca

Institution where the work was performed: McMaster University, Hamilton, Ontario, Canada.

Received: January 25, 2015
Accepted after major revision: April 3, 2015
Epub ahead of print: July 9, 2015
http://dx.doi.org/10.1160/TH15-01-0071
Thromb Haemost 2015; 114: 768–777

Introduction

Despite the increasing interest in personalised medicine, it remains unclear whether genotype-guided dosing of vitamin K antagonists (VKAs) is beneficial. VKAs have a narrow therapeutic index with a risk for significant consequences when out of the therapeutic range (1). Marked inter-patient variability can affect the daily required VKA doses and their variability over time, which is reflected by changes in the time in therapeutic range (TTR). TTR is correlated with clinical events (2-4). A recent European consensus document recommends a TTR of > 70 % when a VKA is used (5). The 2012 Antithrombotic Therapy and Prevention of Thrombosis Guidelines "recommend against the routine use of pharmacogenetic testing for guiding doses of VKA (Grade 1B)" (6).

Observational evidence suggests that genotype-guided VKA dosing algorithms decrease hospitalisations for bleeding and thromboembolism by 28 % at six months (hazard ratio [HR] 0.72, 95 % confidence interval [CI] 0.53–0.97)(7) and TTR at three months by 12 % (absolute) in patients in whom anticoagulation is

initiated (8). *VKORC1* (vitamin K epoxide reductase complex subunit 1) and *CYP2C9* polymorphisms together explain between 30–40 % of the variation in VKA dosage requirement (9). The clinical impact of improving the prediction of dosing requirement is unclear. Randomised controlled trials (RCT) evaluating genotype-guided VKA dosing against standard dosing (non genotype-guided) have yielded conflicting results regarding the impact of genotyping on TTR (10-15). These studies used different genotype-guided algorithms. The approach to standard dosing also varied, some studies used fixed dosing, while others used an algorithm based on clinical characteristics.

A meta-analysis that included nine studies (2,812 patients) did not demonstrate an improvement in TTR (SMD 0.14 %; 95 % CI –0.10, 0.39) (16). The meta-analysis identified considerable heterogeneity for TTR (X^2=68, p< 0.001, I^2=88 %) that was explored in a limited number of subgroup analyses (study quality, study location and sample size) that demonstrated no significant difference in outcomes among those subgroups. The risk ratios for major bleeding and thromboembolic events were not significantly different between the genotype-guided and standard VKA dosing groups. Two other meta-analyses on this topic were recently published (17, 18). The study by Li (10 studies, 2,601 patients) suggests a significant reduction in major bleeding (relative risk [RR] 0.57; 95 % CI: 0.37, 0.90) and thromboembolic events (RR 0.38; 95 % CI: 0.17, 0.85) (17) whereas the one by Franchini (9 trials, 2,812 patients) only suggests a reduction in major bleeding (RR = 0.47, 95 % CI, 0.23–0.96) (18). Neither suggested an improvement in TTR with genotype-guided VKA dosing (MD 4.65%, 95 % CI 0.01, 9.29 and WMD 4.25%; 95 % CI –1.95, 10.45) (18). The considerable heterogeneity for TTR was not explained. None of the published systematic reviews assessed mortality, which is a competing outcome for bleeding and thromboembolism.

We conducted a systematic review and meta-analysis to evaluate the impact on a composite outcome of death, major bleeding and thromboembolic events of genotype-guided VKA dosing algorithms when compared to standard dosing in adults initiating anticoagulation. The components of the composite clinical endpoint, TTR and minor bleeding were evaluated as secondary outcomes.

Methods

The systematic review protocol where selection criteria, primary outcome and secondary outcomes, and plans for statistical analyses were pre-specified is available as Suppl. Material (available online at www.thrombosis-online.com).

Search strategy

We identified relevant references using MEDLINE (1946 to January 2014), EMBASE (1974 to January 2014) and CENTRAL (inception to February 2014). With a medical librarian, we developed a broad search strategy with no language restriction and we used the pre-tested SIGN filters (http://www.sign.ac.uk) to target RCTs (Appendix 1 and 2, in Suppl. Material available online at www.thrombosis-online.com). We reviewed the references of included studies and relevant conference proceedings for 2012 and 2013. We searched clinicaltrials.gov, the ISRCTN Register and WHO ICTRP for unpublished studies.

Study selection

Two independent reviewers screened the retrieved references' titles and abstracts. References deemed potentially relevant by either of the reviewers were included for full text review. To be eligible, studies had to randomise adults requiring the initiation of anticoagulation for any indication to either genotype-guided (*VKORC1* and/or *CYP2C9*) or standard VKA (warfarin, acenocoumarol, dicumarol, phenprocoumon, ethyl biscoumacetate) dosing algorithms. Additionally, studies had to report at least one of the following outcomes: mortality, thromboembolic events, major bleeding, minor bleeding or TTR.

The full text articles of the potentially eligible studies were reviewed independently by two investigators using pre-designed eligibility forms. We contacted the authors of the completed but unpublished trials found in trial registries to obtain their data (Appendix 3, in Suppl. Material available online at www.thrombosis-online.com).

Data extraction and quality assessment

Using a pre-designed data collection spreadsheet, reviewers extracted data in duplicate for each study. Consensus was sought for discordant data.

We contacted the corresponding authors of all included studies to obtain relevant data or to obtain clarification about methods.

Risk of bias was evaluated in duplicate using a modified Cochrane Collaboration risk of bias tool (19). The risk of bias for each evaluation criterion was rated as low, high, or unclear. We considered studies where the clinicians were aware of the study arm as being at high risk of bias given the risk for potential differential reporting of events and influence on international normalised ratio (INR) follow-up. Studies for which the protocol was not available were deemed at low risk of selective outcome reporting if all components of our primary outcome and TTR were reported. For the other potential sources of bias, we evaluated outcome definitions and intention-to-treat analysis.

The quality of evidence for each outcome was evaluated by two reviewers using the GRADE approach (20).

Outcomes

Our primary outcome (defined a priori) was a composite of all cause mortality, thromboembolic events and major bleeding. This approach was used because of the expected low incidence of patient important outcomes during short-term follow-up. Further, improvements in TTR are expected to drive both thrombotic and bleeding event rates in the same direction. Moreover, both of these types of events have a similar impact on mortality (21). For minor

and major bleeding, we used the authors' definitions or, when it was possible to extract this information from the reports, we classified bleeding events as major when they led to hospitalisation or transfusion.

We also evaluated the individual components of our composite outcome, TTR and minor bleeding events. We used the latest TTR (TTR for the longest follow up period) when TTR was reported at more than one time point.

When possible, we applied the intention-to-treat principle by re-introducing in our analyses patients who had been excluded from analysis because they had died during the study period (22, 23).

Statistical analyses

Meta-analyses were performed using Review Manager (RevMan, version 5.2). We used a random effects model to account for the heterogeneity of the included studies. Death, bleeding, thromboembolic events and the primary outcome are reported as RR with 95% CI. Time in the therapeutic range is reported as a mean difference with a 95% CI. Whenever possible, we used TTR calculated using linear interpolation (24). When it was not reported, we used TTR calculated as simple fractions. For a study that reported the number of days within therapeutic range (22), we divided that number by the number of days of follow up to obtain a TTR that could be pooled. A 5% significance level was used for all analyses.

Heterogeneity was evaluated by visual inspection of the forest plots and using $\chi 2$ statistics. Chance independent heterogeneity between studies was evaluated using the I^2 method (25) and was categorised using a standard classification (42). In the presence of heterogeneity, data were verified. Potential clinical and methodological causes of heterogeneity were also explored using pre-specified subgroup analyses. Dosing algorithm in the standard arm (fixed dosing vs clinical algorithm-guided), proportion of non-Caucasian participants (< 10% vs > 10%) and risk of bias (low risk of bias vs moderate and high risk of bias) were evaluated as interaction terms.

We evaluated publication bias using a funnel plot of effect size vs standard error for TTR. Too few studies (< 10) were included in our assessment of the other outcomes to generate meaningful funnel plots (26).

Sensitivity analyses

For the primary outcome, we conducted a "plausible worst-case scenario sensitivity analysis" hypothesizing a five times higher event rate in the patients lost to follow up (27). Given the unexpected important number of patients randomised but not analysed

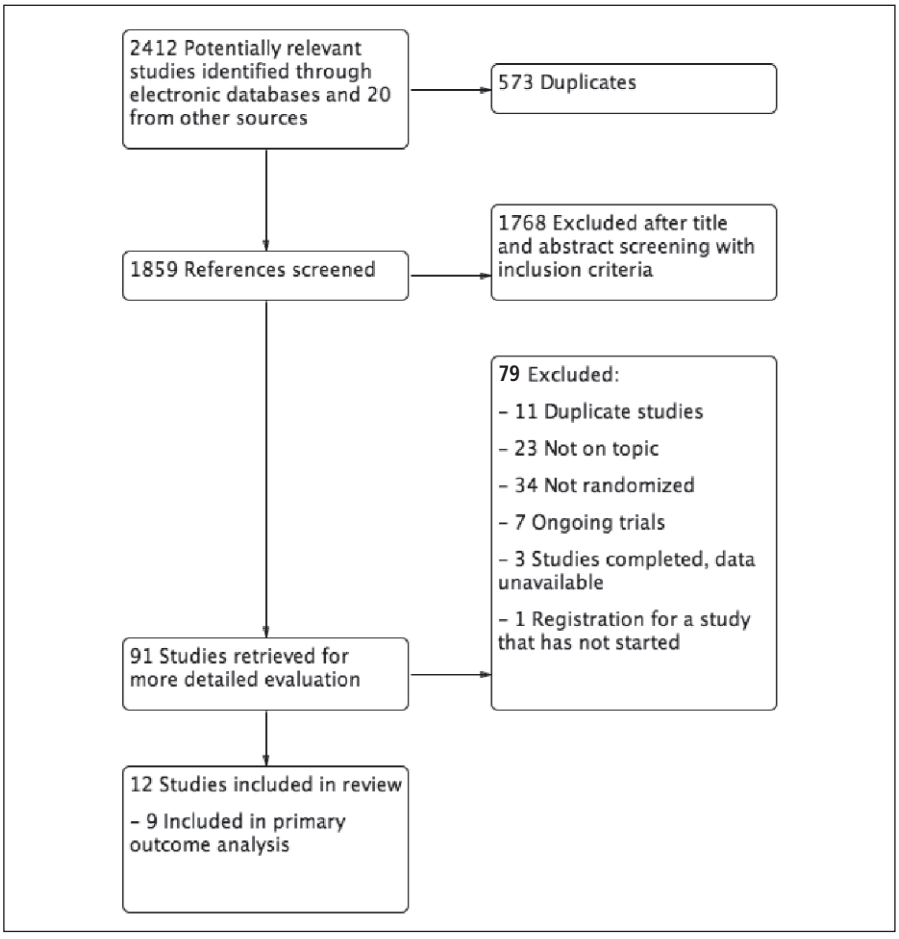

Figure 1: Flow of studies included in review.

Table 1: Characteristics of included studies.

Study	VKA	Sample size	Caucasian N (%)	Age (years) Mean (SD)	% CYP2C9 variants GG/S	VKCOR Mer variants % GG/%S	Therapeutic range definition	Follow up duration	Standard arm dosing	Risk of bias
Hillman 2005 (15)	warfarin	38	30 (100)	69.7 (12.3)	38.9/35	NA	NA	28 days	5 mg daily	high
Anderson 2007 (30)	warfarin	206	189 (92)	61.1 (10.6)	NA	49.5/63.3	1.8–3.2	3 months	Kovacs (40)	high
Caraco 2007 (29)	warfarin	283	NA	58.7 (14.1)	36.8/46.9	NA	1.8–3.4	Variable	DAWN AC (41)	high
Huang 2009 (22)	warfarin	142	0 (0)	42.3 (10.2)	6.6/3.3	18/13.3	1.8–3.0	50 days	2.5 mg daily	high
Burmester 2011 (28)	warfarin	230	230 (100)	68.3 (8.3)	36/40.2	54.4/64.3	NA	60 days	Clinical algorithm-guided	high
Borgman 2012 (10)	warfarin	34	24 (71)	52 (12.1)	31/38	46/62	1.8–3.2	3 months	Kovacs (40)	high
Radhakrishnan 2012 (31)	warfarin	56	NA	NA	28/28	52/57	NA	3 months	NA	high
Wang 2012 (23)	warfarin	101	0 (0)	42.4 (7.5)	4/4	12/20	1.8–3.0	50 days	2.5 mg daily	high
Jonas 2013 (14)	warfarin	109	79 (72)	57.2 (19.2)	39.6/25.5	49.1/60.8	1.8–3.2 2.3–3.7	3 months	Clinical algorithm-guided	high
Kimmel 2013 (12)	warfarin	1015	* 67 % or less	58 (16.3)	NA	51/53	2.0–3.0	6 months	Clinical algorithm-guided	low
Pirmohamed 2013 (11)	warfarin	455	421 (98.6)	67.5 (13.5)	33.6/33.8	59.7/56.1	2.0–3.0	3 months	Fixed doses determined by age	high
Verhoef 2013 (13)	acenocoumarol and phencoupron	548	533 (97.2 %)	68 (13)	39/40	66/68	2.0–3.0	3 months	Clinical algorithm-guided	high

* Kimmel reports Black vs non-Black, not Caucasians. N : Number. SD : Standard Deviation. GG : Genotype-guided. S : Standard. NA : Not Available.

and the difficulty separating them from the patients lost to follow-up in some papers, we conducted a post-hoc sensitivity analysis hypothesising a five times higher event rate in the highest of either the number of patients randomised but not analysed or the number of patients lost to follow-up.

We conducted a post hoc sensitivity analysis to assess the consistency of results when pooling the earliest TTR reported when TTR was reported at more than one time point during a study.

Results

Literature search

The search strategy identified 2,412 references (►Figure 1). After reviewing citations, 12 published studies (3,217 patients) were included with a κ for agreement of 1.0 (0.75–1.00). Through the trial registries, we identified seven ongoing trials and three that were completed but not yet published. The authors of the latter were contacted and they indicated that they were either analyzing their results or in the submission process (Appendix 3, in Suppl. Material available online at www.thrombosis-online.com).

Study characteristics and risk of bias

The 12 included RCTs are described in ►Table 1. The follow-up duration ranged from 28 days to six months. Nine studies included patients with different indications for anticoagulation (10-15, 28-30) and two studies focused on patients with mechanical valve prostheses (22, 23). The indication for anticoagulation was not available for one trial that is currently only published as an abstract (31).

Only one trial was at low risk of bias (12), all others had high risk of bias (►Figure 2). Caraco et al. used pseudo-randomisation using chart numbers and evaluated outcomes over different lengths of follow-up in each study group (29). Reporting of allocation concealment was inconsistent. Only one study blinded par-

ticipants, clinicians, research personnel and outcome assessors (12). Patients who died during the study period were excluded from analysis in two trials (22, 23). Three studies did not report any of the three components of the primary outcome (29-31). Loss to follow-up was significant in three studies: 23% in the study by Borgman (10), 16% in the study by Caraco (29) and 12% in the study by Verhoef (13). Five studies did not report the definitions used for bleeding events (10, 15, 22, 23, 31). The inter-evaluator agreement for risk of bias was near perfect with a weighted κ of 0.90.

Primary outcome

Six studies (2,223 patients) reported all components of the primary outcome. When the studies were pooled, there were 39 events in the genotype-guided group and 48 events in the standard group. The RR for the composite of mortality, major bleed and thromboembolic events was 0.85 (95% CI 0.54–1.34, p=0.48). There was very low heterogeneity as evaluated by a X^2=4.46 (p=0.35) and an I^2 of 10% (►Figure 3).

These results were unchanged when sensitivity analyses were conducted using a "plausible worst-case scenario sensitivity analysis".

Subgroup analyses did not demonstrate significant interaction between randomised intervention and dosing strategy in the standard group (X^2=0.12, p=0.73), proportion of Caucasian participants (X^2=0.94, p=0.33) and risk of bias (X^2=0.16, p=0.69).

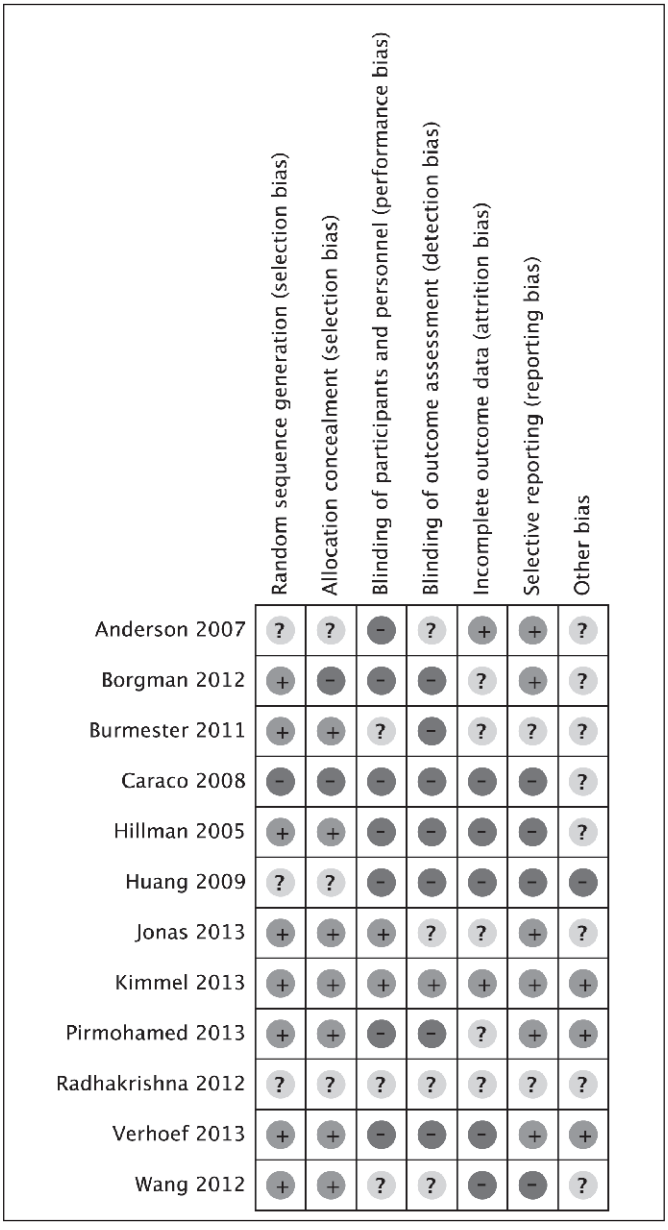

Figure 2: Risk of bias summary.

Individual components of the primary outcome: mortality, major bleeding and thromboembolic events

Eight studies (2,449 patients) evaluated mortality. Eleven patients died in the genotype-guided arm and ten in the standard dosing arm. There was no significant difference between groups: RR 1.12 (95% CI 0.46–2.74, p=0.80; heterogeneity X^2=3.61, p=0.61, I^2=0%).

Nine studies (2,567 patients) reported major bleeding. There were 17 major bleeding episodes in the genotype-guided arm and 26 in the standard dosing arm. There was no significant difference between the groups RR 0.71 (95% CI 0.38–1.29, p=0.26; heterogeneity X^2=4.0, p=0.40, I^2=0%).

Seven studies (2,261 patients) reported thromboembolic events. Thirteen thromboembolic events occurred in the genotype-guided arm and 20 in the standard dosing arm. There was no significant difference between the groups RR 0.74 (95% CI 0.37–1.49, p=0.60; heterogeneity X^2=3.69, p=0.60, I^2=0%).

Time in the therapeutic range

Ten studies (2,767 patients) reported time in therapeutic range (TTR). Two reported TTR as a simple fraction, seven reported TTR using linear interpolation and TTR (simple fraction) had to be calculated for one study (Appendix 4, in Suppl. Material available online at www.thrombosis-online.com). There was a statistically significant improvement in TTR in the genotype-guided group (MD 4.31%, 95% CI 0.35–8.26, p=0.03). There was substantial heterogeneity (X^2=43.31, p<0.001, I^2=79%). Visual inspection of the forest plot confirmed heterogeneity (►Figure 4). The funnel plot was symmetrical and did not suggest a publication bias.

We evaluated pre-specified subgroups to try to explain heterogeneity in TTR. The dosing strategy in the standard group was a significant interaction term with TTR (X^2=10.07, p=0.002). Although heterogeneity remained substantial in the fixed dosing group (X^2=15.18, p=0.01, I^2=67%), it was not observed in the clinical algorithm-guided group (X^2=1.53, p=0.68, I^2=0%). TTR was significantly higher with genotype-guiding when compared with fixed dosing (MD 8.41%, 95% CI 3.50–13.31, p<0.001). There was no statistically significant difference when genotyping

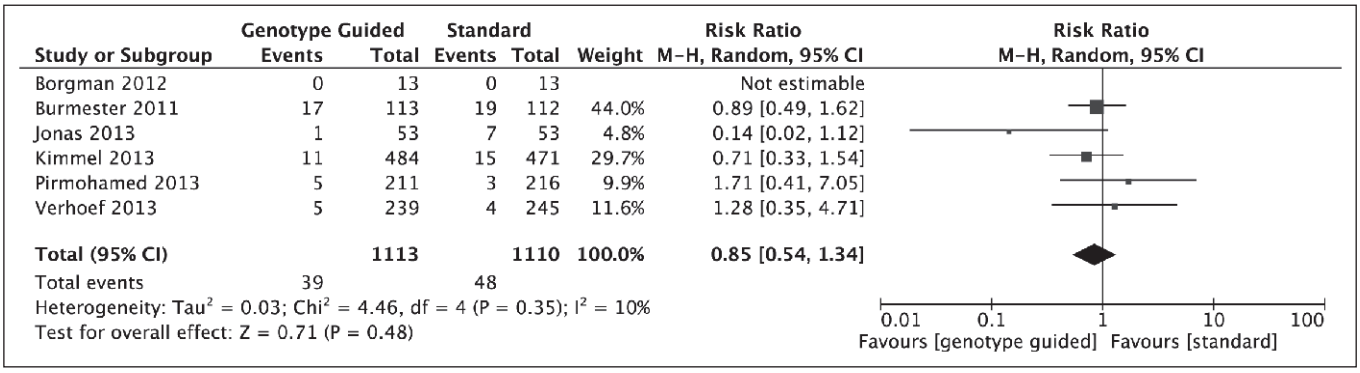

Figure 3: Forest plot for the composite of mortality, major bleed and thromboembolic events.

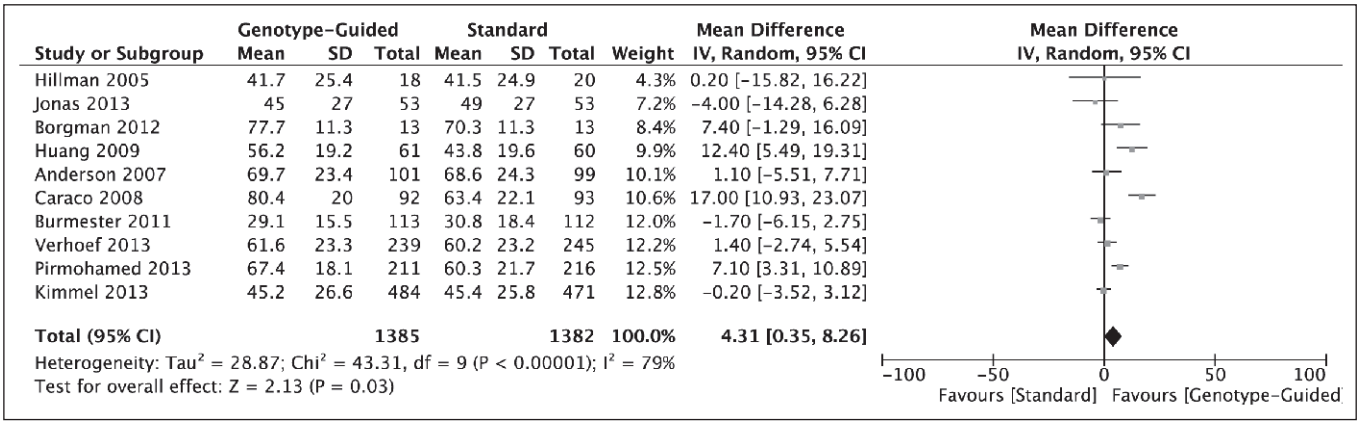

Figure 4: Time in therapeutic range using the latest TTR.

was compared with clinical algorithm-guided dosing (MD -0.29%, 95% CI -2.48–1.90, p=0.80) (▶Figure 5). Proportion of non-Caucasians (X^2=0.22, p=0.64) and risk of bias (X^2=3.31, p=0.07) were not significant interaction terms.

In a post-hoc sensitivity analysis, when using the earliest TTR for studies reporting TTR at more than one time point, the results proved to be robust with a MD 5.45% (for all studies: 95% CI 0.41–10.49, p=0.03; heterogeneity X^2=70.5, p<0.001, I^2=87%).

Minor bleeding

Minor bleeding was reported in seven studies (2,468 patients). A total of 443 events occurred in the genotype-guided arm and 475 in the standard dosing arm. There was no significant difference between groups for minor bleeding (RR 0.87, 95% CI 0.64–1.19, p=0.38). Heterogeneity was considerable (X^2=58.83, p<0.00001, I^2=92%) (▶Figure 6).

Subgroup analyses demonstrated that risk of bias and the proportion of non-Caucasians were not effect modifiers (X^2=0.90, p=0.34 and X^2=0.07, respectively, p=0.79). The dosing strategy used in the standard group was a significant interaction term (X^2=19.97, p<0.00001, ▶Figure 6B). The subgroup of studies using fixed dosing in the standard arm demonstrated a significantly lower risk of minor bleeding associated with genotype-guided dosing RR 0.47 (95% CI 0.34–0.65, p<0.00001). There was no heterogeneity for this subgroup (X^2=0.15, p=0.7, I^2=0%). The subgroup of studies using clinical algorithms demonstrated no significant difference in minor bleeding RR 0.87 (95% CI 0.64–1.19, p=0.38). Heterogeneity remained considerable for this outcome (X^2=58.83, p<0.00001, I^2=92%).

We did not conduct some of the a priori stated subgroup analyses for different reasons: we could not extract the individual patient data from the reports (indication for anticoagulation), there were no studies in one subgroup (non-trial based anticoagulation management in the control group) and only one of the studies (n=38) had a follow up of less than one month (duration of follow-up).

Quality of evidence

Using the GRADE approach, we downgraded the quality of evidence for each outcome. Risk of bias was downgraded for all outcomes due to lack of allocation concealment, inadequate post randomisation exclusions, absence of validated outcome definitions, selective outcome reporting and significant loss to follow up in many of the included studies. Absence of blinding was also an issue except for the mortality outcome. Unexplained heterogeneity required downgrading for inconsistency for TTR and minor bleeding. TTR, because it is a surrogate outcome, was downgraded for indirectness. The results for mortality, major

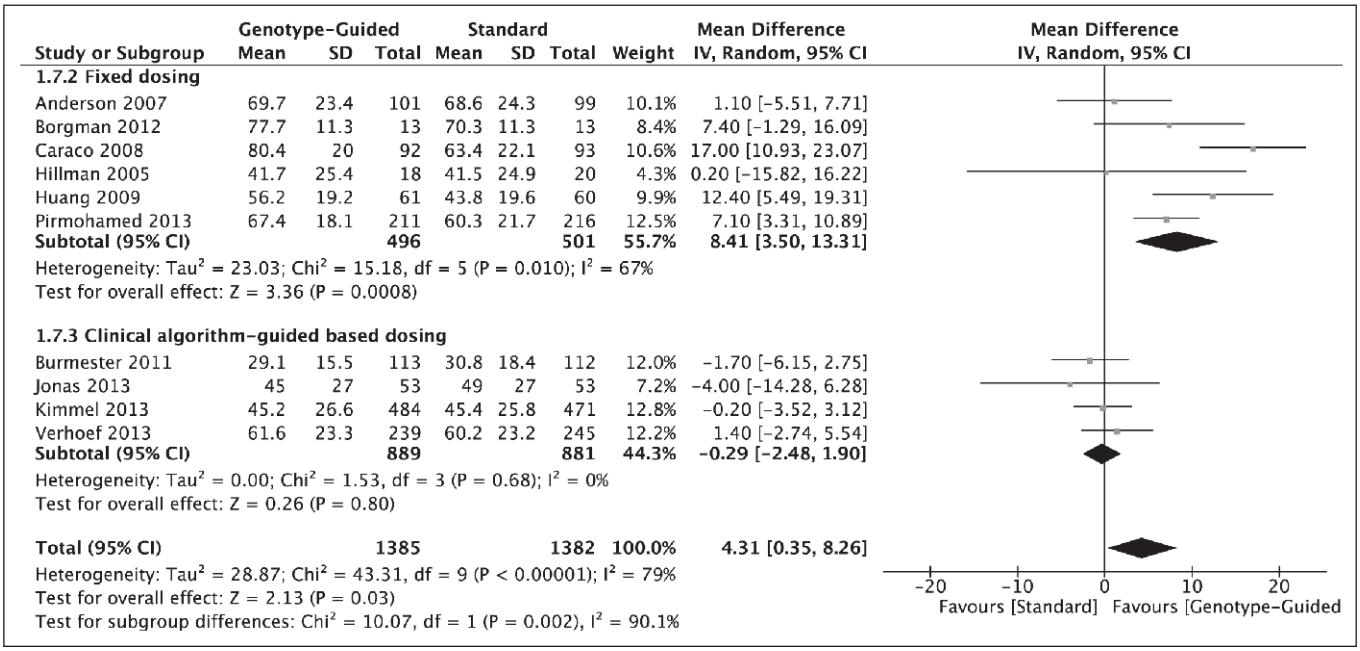

Figure 5: Time in therapeutic range – subgroup analysis according to the type of dosing regimen in the standard group.

bleeding, thromboembolic events and for the composite outcome were imprecise and included both significant harm and benefit. The estimates for TTR and minor bleeding were more precise but included no effect and significant benefit for minor bleeding.

Discussion

In this meta-analysis of RCTs, genotype-guided VKA dosing algorithms did not significantly decrease the incidence of a composite outcome of death, major bleeding and thromboembolic events. The evidence supporting this is of very low quality based on the GRADE criteria (20). Death, major bleeding, minor bleeding and thromboembolic events when evaluated individually were also similar in both groups, supported by very low quality evidence. Based on low quality evidence, TTR was significantly higher in the genotype-guided arm, particularly when compared to a fixed dosing approach to warfarin management.

Our results regarding clinical outcomes are similar to those in the previous meta-analysis by Stergiopoulos (16). However, we demonstrated an improvement in TTR with genotype-guided VKA dosing. This may be attributable to an increased power because we identified three additional trials. By including additional studies our results not only increase confidence in the estimates of effect, but our a priori defined subgroup analyses yielded hypotheses generating results that may explain the heterogeneity for the pooled estimate of the mean difference for TTR.

The other two published meta-analyses suffer from methodological issues that threaten the validity of their results (17, 18). Li et al. included an observational study in their systematic review of RCTs (32). They also limited their review to warfarin, excluding the second largest trial evaluating the efficacy of genotype-guided VKA dosing (13). The results presented by Franchini et al. (18) are fragile. There were only 10 events in the genotype-guided group compared to 21 in the standard dosing group, and adding a single event to the genotyping group would have eliminated the statistical significance. Given that there were losses to follow-up in many of the studies, missed events represent a real threat to their findings. Moreover, the assumptions made to retrieve major bleeding events within the included studies are probably wrong with major bleeding incidence rates that reach 13.2% at 28 days for one study. This incidence is inconsistent with the major bleeding incidence in anticoagulation studies that is about 3.4% (33) and with the incidence in the largest trial comparing genotype-guided with standard VKA dosing where major bleeding was clearly defined and captured as a secondary outcome [1.4% (14/1015) at 28 days] (12).

Strengths and limitations

Bias was minimised by a priori protocol elaboration, use of a broad literature search focusing on RCTs and double data extraction. We assessed important clinical outcomes and evaluated the quality of evidence using the GRADE approach.

To increase power, we pooled studies broadly, thus potentially introducing methodological heterogeneity. The included studies focused on different populations, used distinct algorithms, different outcome definitions and different lengths of follow up. This heterogeneity may not be reflected in the statistical evaluation for heterogeneity for the primary outcome because of the low sensitivity of the X^2 test and, in consequence, of the I^2 test.

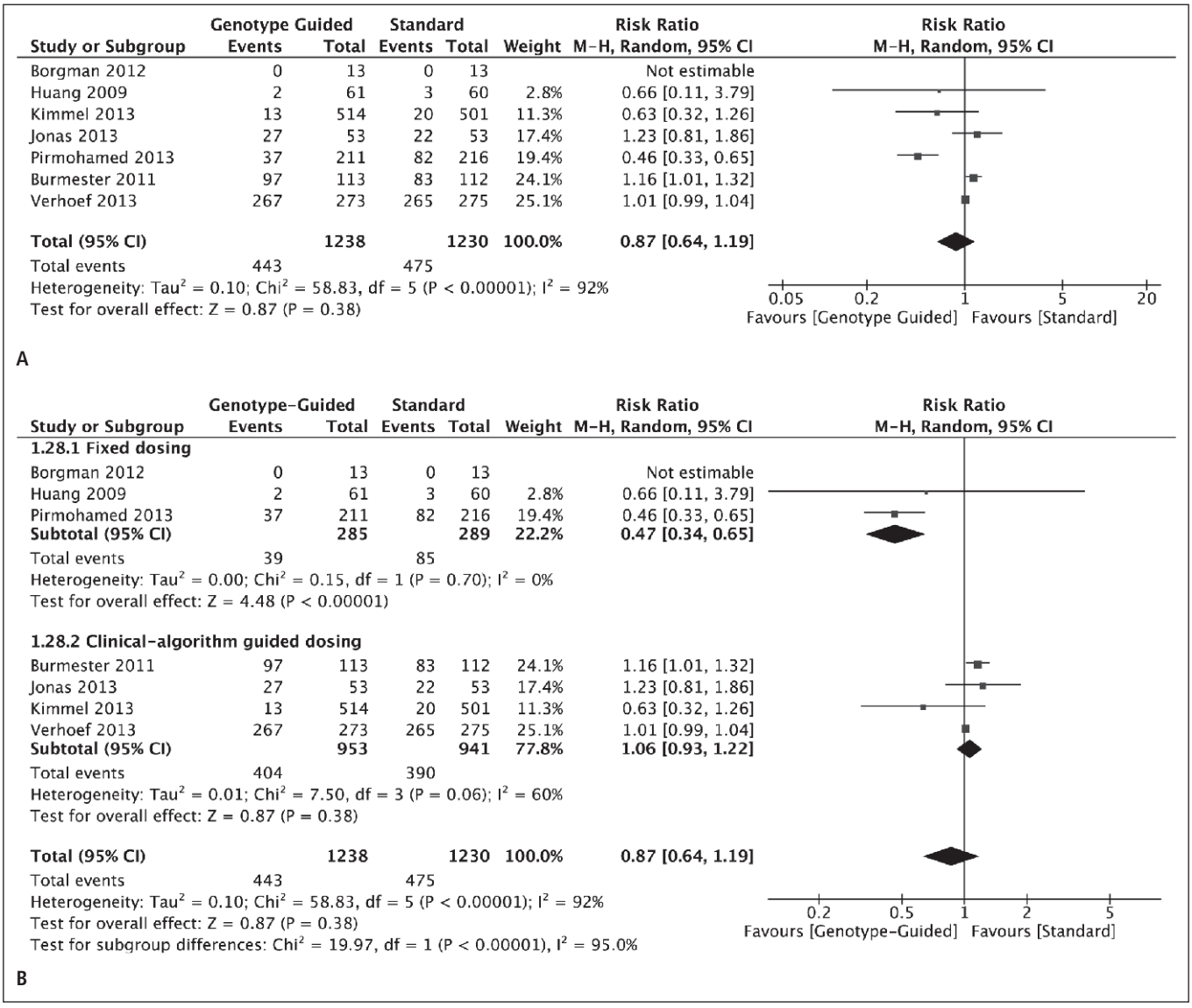

Figure 6: Minor bleeding. A) Overall results. B) Subgroup analysis according to type of dosing regimen in the standard group.

Sample size and surrogate outcomes

Despite 2,483 patients contributing to this meta-analysis, there is limited power with only 87 events. This 3.9% event rate is expected in patients initiating anticoagulation with a follow-up varying between 28 days and six months. Using data from recent anticoagulation studies in atrial fibrillation (33) and deep venous thrombosis populations (34), the combined incidence of mortality, major bleeding and thromboembolic events over six months in the warfarin arm is about 4.3%. The optimal information size (OIS) to detect a 20% relative risk reduction (RRR) with a three month follow-up would require over 16,000 patients per study arm with 80% power and a two-sided α of 0.05. If the patients were to be followed for a year, the OIS to detect a 20% RRR would be 3,835 patients per study arm (36). One approach to reducing sample size would be to power a study to detect a higher RRR. However, a reduction in stroke of 1% was demonstrated to be clinically important to patients (35). A 20% RRR in our composite endpoint represents an absolute reduction in mortality and stroke of about 1%.

Decreased TTRs have been associated with increased mortality, stroke, bleeding and thromboembolic event rates (3, 36). The improvement in anticoagulant treatment effect seen with increased TTR is independent of the patients' baseline characteristics (2). However, statistically significant changes in TTR may not translate in significant changes in the patient outcomes (37). A statistical simulation has suggested that a 25% absolute increase in TTR was required to translate to an absolute 1% decrease in adverse events (38).

Given the higher rate of minor bleeding, we would have expected the improvement in TTR seen in the genotype-guided group to be mirrored by an improvement in this event. However, poor capturing of adverse events in studies where they are not predefined outcomes and use of different outcome definitions may have contributed. The variability in the incidence of reported minor bleeding events across studies [from <5% (22) to >95%(13)] makes pooling questionable and probably explains the considerable heterogeneity for this outcome.

Studies using fixed VKA dosing algorithms in the standard arm were associated with both a greater improvement in TTR and a decrease in minor bleeding. Subgroups analyses should be considered hypothesis generating (39). However, consistency across related outcomes increases the plausibility of a true subgroup effect (39). Moreover, this effect is in the same direction as our a priori stated hypothesis (39). Fixed initial VKA dosing with decision support tools during maintenance is currently the recommended approach for outpatient anticoagulation initiation (6). To our knowledge, fixed VKA dosing algorithms have not been compared to clinical algorithm-guided VKA dosing. This is an area that could be explored in future trials.

Heterogeneity

Because of the high heterogeneity that is only partially explained by subgroup effects, pooling of TTRs could be questioned, especially in light of their wide range (29–80%). Duration of follow-up and various calculation methods could account for some of this heterogeneity but were not explored because they had not been pre-specified.

The differences in the genotype-guided algorithms is another major source of heterogeneity. Some algorithms include more variables or have undergone more validation than others and may perform better. Since each study used a different algorithm, it was not possible to conduct subgroup analyses.

What is known about this topic?

- Genotype-guided vitamin K antagonist (VKA) dosing may be beneficial.
- Published randomised controlled trials (RCTs) have yielded conflicting results regarding the impact on time in therapeutic range (TTR).
- These RCTs were underpowered for the evaluation of clinical events.

What does this paper add?

- Genotype-guided VKA dosing did not improve a composite of death, thromboembolism and major bleeding.
- Genotype-guided VKA dosing improved TTR.
- Improvement in TTR was observed in comparison with fixed VKA dosing algorithms, but not with clinical algorithms.

Conclusion

Based on very low quality of evidence, genotype-guided VKA dosing algorithms do not decrease a composite of mortality, major bleeding and thromboembolic events. The estimates of risk cannot exclude a significant benefit nor harm. Even pooled, the studies remain underpowered for the detection of a significant difference in clinical events. TTR was significantly higher in the genotype-guided arm and suggests that larger studies might demonstrate a benefit on clinical events.

Acknowledgements

Jo-Anne Petropoulos for her help with the building of our search strategy.

Conflicts of interest

J. W. Eikelboom has received grants and/or personal fees from Bayer, Boehringer Ingelheim, AstraZeneca, BMS, GSK, Pfizer, Janssen, Sanofi-Aventis, Daiichi-Sankyo, and Eli Lilly (all outside the submitted work). S. E. Kimmel has received personal fees from Pfizer and Janssen (all outside the submitted work). A. H. Maitland-van der Zee has received grants from the European Commission FP7 Collaborative Grant EU-PACT during the conduct of this study. M. Pirmohamed has received grants from the EU Commission during the conduct of this study. None of the other authors declares and conflicts of interest.

References

1. Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in outpatients taking warfarin. Ann Intern Med 1994; 120: 897–902.
2. Connolly SJ, Pogue J, Eikelboom J, et al. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. Circulation 2008; 118: 2029–2037.
3. Veeger NJ, Piersma-Wichers M, Tijssen JG, et al. Individual time within target range in patients treated with vitamin K antagonists: main determinant of quality of anticoagulation and predictor of clinical outcome. A retrospective study of 2300 consecutive patients with venous thromboembolism. Br J Haematol 2005; 128: 513–519.
4. Gallego P, Roldan V, Marin F, et al. Cessation of oral anticoagulation in relation to mortality and the risk of thrombotic events in patients with atrial fibrillation. Thromb Haemost 2013; 110: 1189–1198.
5. De Caterina R, Husted S, Wallentin L, et al. Vitamin K antagonists in heart disease: current status and perspectives (Section III). Position paper of the ESC Working Group on Thrombosis--Task Force on Anticoagulants in Heart Disease. Thromb Haemost 2013; 110: 1087–1107.
6. Guyatt GH, Akl EA, Crowther M, et al., American College of Chest Physicians Antithrombotic T, et al. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141 (2 Suppl): 7S-47S.
7. Epstein RS, Moyer TP, Aubert RE, et al. Warfarin genotyping reduces hospitalization rates results from the MM-WES (Medco-Mayo Warfarin Effectiveness study). J Am Coll Cardiol 2010; 55: 2804–2812.
8. Anderson JL, Horne BD, Stevens SM, et al. A randomized and clinical effectiveness trial comparing two pharmacogenetic algorithms and standard care for individualizing warfarin dosing (CoumaGen-II). Circulation 2012; 125: 1997–2005.
9. Wadelius M, Chen LY, Lindh JD, et al. The largest prospective warfarin-treated cohort supports genetic forecasting. Blood 2009; 113: 784–792.

10. Borgman MP, Pendleton RC, McMillin GA, et al. Prospective pilot trial of PerMIT versus standard anticoagulation service management of patients initiating oral anticoagulation. Thromb Haemost 2012; 108: 561–569.
11. Pirmohamed M, Burnside G, Eriksson N, et al. A randomized trial of genotype-guided dosing of warfarin. N Engl J Med 2013; 369: 2294–2303.
12. Kimmel SE, French B, Kasner SE, et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. N Engl J Med 2013; 369: 2283–2293.
13. Verhoef TI, Ragia G, de Boer A, et al. A randomized trial of genotype-guided dosing of acenocoumarol and phenprocoumon. N Engl J Med 2013; 369: 2304–2312.
14. Jonas DE, Evans JP, McLeod HL, et al. Impact of genotype-guided dosing on anticoagulation visits for adults starting warfarin: a randomized controlled trial. Pharmacogenomics 2013; 14: 1593–1603.
15. Hillman MA, Wilke RA, Yale SH, et al. A prospective, randomized pilot trial of model-based warfarin dose initiation using CYP2C9 genotype and clinical data. Clin Med Res 2005; 3: 137–145.
16. Stergiopoulos K, Brown DL. Genotype-Guided vs Clinical Dosing of Warfarin and Its Analogues: Meta-analysis of Randomized Clinical Trials. J Am Med Assoc Intern Med 2014; 174: 1330–1338.
17. Li X, Yang J, Wang X, et al. Clinical benefits of pharmacogenetic algorithm-based warfarin dosing: meta-analysis of randomized controlled trials. Thromb Res 2015; Epub ahead of print.
18. Franchini M, Mengoli C, Cruciani M, et al. Effects on bleeding complications of pharmacogenetic testing for initial dosing of vitamin K antagonists: a systematic review and meta-analysis. J Thromb Haemost 2014; 12: 1480–1487.
19. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Br Med J 2011; 343: d5928.
20. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011; 64: 401–406.
21. Wu C, Alotaibi GS, Alsaleh K, et al. Case fatality of bleeding and recurrent venous thromboembolism during, initial therapy with direct oral anticoagulants: A systematic review. Thromb Res 2014; Epub ahead of print.
22. Huang SW, Chen HS, Wang XQ, et al. Validation of VKORC1 and CYP2C9 genotypes on interindividual warfarin maintenance dose: a prospective study in Chinese patients. Pharmacogenet Genomics 2009; 19: 226–234.
23. Wang M, Lang X, Cui S, et al. Clinical application of pharmacogenetic-based warfarin-dosing algorithm in patients of Han nationality after rheumatic valve replacement: a randomized and controlled trial. Intern J Med Sci 2012; 9: 472–479.
24. Rosendaal FR, Cannegieter SC, van der Meer FJ, et al. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993; 69: 236–239.
25. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics Med 2002; 21: 1539–1558.
26. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol 2000; 53: 1119–1129.
27. Akl EA, Briel M, You JJ, et al. Potential impact on estimated treatment effects of information lost to follow-up in randomised controlled trials (LOST-IT): systematic review. Br Med J 2012; 344: e2809.
28. Burmester JK, Berg RL, Yale SH, et al. A randomized controlled trial of genotype-based Coumadin initiation. Genetics Med 2011; 13: 509–518.
29. Caraco Y, Blotnick S, Muszkat M. CYP2C9 genotype-guided warfarin prescribing enhances the efficacy and safety of anticoagulation: a prospective randomized controlled study. Clin Pharmacol Therap 2008; 83: 460–470.
30. Anderson JL, Horne BD, Stevens SM, et al. Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. Circulation 2007; 116: 2563–2570.
31. Radhakrishnan A, Vido D, Tayur S, et al. Genotype Guided Therapeutic Dosing of Warfarin in Geriatric Patients. J Am Coll Cardiol 2012; 59: E1696.
32. McMillin GA, Melis R, Wilson A, et al. Gene-based warfarin dosing compared with standard of care practices in an orthopedic surgery population: a prospective, parallel cohort study. Therap Drug Monitor 2010; 32: 338–345.
33. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361: 1139–1151.
34. Investigators E, Bauersachs R, Berkowitz SD, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010; 363: 2499–2510.
35. Man-Son-Hing M, Laupacis A, O'Connor A, et al. Warfarin for atrial fibrillation. The patient's perspective. Arch Intern Med 1996; 156: 1841–1848.
36. Jones M, McEwan P, Morgan CL, et al. Evaluation of the pattern of treatment, level of anticoagulation control, and outcome of treatment with warfarin in patients with non-valvar atrial fibrillation: a record linkage study in a large British population. Heart 2005; 91: 472–477.
37. Matchar DB, Jacobson A, Dolor R, et al. Effect of home testing of international normalized ratio on clinical events. N Engl J Med 2010; 363: 1608–1620.
38. van Walraven C, Oake N, Coyle D, et al. Changes in surrogate outcomes can be translated into clinical outcomes using a Monte Carlo model. J Clin Epidemiol 2009; 62: 1306–1315.
39. Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. Br Med J 2010; 340: c117.
40. Kovacs MJ, Rodger M, Anderson DR, et al. Comparison of 10-mg and 5-mg warfarin initiation nomograms together with low-molecular-weight heparin for outpatient treatment of acute venous thromboembolism. A randomized, double-blind, controlled trial. Ann Intern Med 2003; 138: 714–719.
41. Ageno W, Johnson J, Nowacki B, et al. A computer generated induction system for hospitalized patients starting on oral anticoagulant therapy. Thromb Haemost 2000; 83: 849–852.
42. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

