Meta-analysis of Randomized Controlled Trials of Genotype-Guided vs Standard Dosing of Warfarin

Khagendra Dahal, MD; Sharan P. Sharma, MD; Erik Fung, MD, PhD; Juyong Lee, MD, PhD; Jason H. Moore, PhD; John N. Unterborn, MD; and Scott M. Williams, PhD

BACKGROUND: Warfarin is a widely prescribed anticoagulant, and its effect depends on various patient factors including genotypes. Randomized controlled trials (RCTs) comparing genotype-guided dosing (GD) of warfarin with standard dosing have shown mixed efficacy and safety outcomes. We performed a meta-analysis of all published RCTs comparing GD vs standard dosing in adult patients with various indications of warfarin use.

METHODS: We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and relevant references for English language RCTs (inception through March 2014). We performed the meta-analysis using a random effects model.

RESULTS: Ten RCTs with a total of 2,505 patients were included in the meta-analysis. GD compared with standard dosing resulted in a similar % time in therapeutic range (TTR) at ≤ 1 month follow-up (39.7% vs 40.2%; mean difference [MD], -0.52 [95% CI, -3.15 to 2.10]; $P = .70$) and higher % TTR (59.4% vs 53%; MD, 6.35 [95% CI, 1.76 - 10.95]; $P = .007$) at > 1 month follow-up, a trend toward lower risk of major bleeding (risk ratio, 0.46 [95% CI, 0.19 - 0.111]; $P = .08$) at ≤ 1 month follow-up and lower risks of major bleeding (0.34 [95% CI, 0.16 - 0.74], $P = .006$) at > 1 -month follow-up, and shorter time to maintenance dose (TMD) (24.6 days vs 34.1 days; MD, -9.54 days [95% CI, -18.10 to -0.98]; $P = .03$) at follow-up but had no effects on international normalized ratio [INR] > 4.0 , nonmajor bleeding, thrombotic outcomes, or overall mortality.

CONCLUSIONS: In the first month of genotype-guided warfarin therapy, compared with standard dosing, there were no improvements in % TTR, INR > 4.0 , major or minor bleeding, thromboembolism, or all-cause mortality. There was a shorter TMD, and, after 1 month, improved % TTR and major bleeding incidence, making this a cost-effective strategy in patients requiring longer anticoagulation therapy.

CHEST 2015; 148(3):701-710

Manuscript received November 25, 2014; revision accepted March 2, 2015; originally published Online First March 26, 2015.

ABBREVIATIONS: GD = genotype-guided dosing; HR = hazard ratio; INR = international normalized ratio; MD = mean difference; RCT = randomized controlled trial; RR = risk ratio; TMD = time to maintenance dose; TTR = time in therapeutic range

AFFILIATIONS: From the Department of Medicine (Dr Dahal), LRGHealthcare, Laconia, NH; the Department of Medicine (Dr Sharma), Englewood Hospital and Medical Center, Englewood, NJ; the Section of Cardiology, Heart and Vascular Center (Dr Fung), and the Norris Cotton Cancer Center (Drs Moore and Williams), Dartmouth-Hitchcock Medical Center, Lebanon, NH; the Geisel School of Medicine (Drs Fung and Moore), the Department of Genetics (Drs Moore and Williams), and the Institute of Quantitative Biomedical Science (Drs Moore and

Williams), Dartmouth College, Hanover, NH; the Calhoun Cardiology Center (Dr Lee), University of Connecticut Health Center, Farmington, CT; and the Department of Medicine (Dr Unterborn), St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, MA.

FUNDING/SUPPORT: The authors have reported to *CHEST* that no funding was received for this study.

CORRESPONDENCE TO: Khagendra Dahal, MD, Department of Internal Medicine, LRGHealthcare, 80 Highland St, Laconia, NH 03246; e-mail: kdahal@lrgh.org

© 2015 AMERICAN COLLEGE OF CHEST PHYSICIANS. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details.

DOI: 10.1378/chest.14-2947

The US Food and Drug Administration has estimated that 2 million patients are initiated on anticoagulation warfarin therapy annually in the United States.¹ Because warfarin has a narrow therapeutic range as measured by international normalized ratio (INR),² and being outside of the therapeutic range in either direction can have devastating effects, appropriate dosing is a major clinical issue; a subtherapeutic INR increases risk of thrombosis, whereas a supratherapeutic INR increases bleeding risk with associated morbidity and mortality.³ Of note, warfarin toxicity has been reported to account for > 10% of all adverse drug reactions leading to hospital admission.⁴

Warfarin works by inhibiting the C1 subunit of vitamin K epoxide reductase enzyme (encoded by *VKORC1*) and by interfering with cyclic interconversion of vitamin K⁵ essential for the activation of vitamin K-dependent clotting factors such as II, VII, IX, and X as well as endogenous anticoagulant factors, protein C, and protein S.⁶ Clinically available warfarin is a racemic molecule, which presents as *S*-warfarin and *R*-warfarin.⁷ *S*-warfarin, compared with *R*-warfarin, is approximately five times more active as a VKOR inhibitor and is converted to

inactive metabolites by CYP2C9, encoded by *CYP2C9*.⁴ Several polymorphisms of *CYP2C9* have been identified that decrease the activity of the enzyme.⁸

Interindividual variations in warfarin dose requirement are highly variable.^{9,10} Data suggest that at least 50% of the variance in dose requirements can be accounted for by a combination of age, ethnicity, body weight, and genetic polymorphisms in *VKORC1* and *CYP2C9*.^{9,11-13} Studies have demonstrated that patients with allelic variants in *CYP2C9* and *VKORC1* require significantly different warfarin doses than those with wild-type alleles.^{9,14-16} Because of the critical nature of appropriate personal dosing and the role that genetics may play in dose responses, several pharmacogenetic-based dosing algorithms have been developed for warfarin.⁹ However, randomized trials comparing genotype-guided dosing (GD) of warfarin vs standard dosing have shown mixed outcomes.¹⁷⁻¹⁹ To better assess whether the genetic tests actually improve warfarin dosing targeting, we performed a meta-analysis of currently available randomized controlled trials (RCTs) that compared GD with standard dosing in adult patients (≥ 18 years) with various indications for warfarin use.

Materials and Methods

Data Sources and Search Strategy

The meta-analysis was performed with a study protocol written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.²⁰ We searched MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) for English language publications from inception through March 2014. The search terms were “genotypes” or “pharmacogenetics” or “pharmacogenomics” and “warfarin” and “dosing” or “initiation” or “maintenance” with restriction to randomized study designs. Database search was independently performed by two researchers (K. D. and S. P. S.), and disagreement was resolved by consensus. ClinicalTrials.gov was also searched for past or ongoing trials of interest. A manual search was performed for all relevant references including published reviews and meta-analyses. The flow diagram for study selection is shown (Fig 1).

Study Inclusion and Exclusion Criteria

RCTs of warfarin comparing GD to standard dosing in adults ≥ 18 years old with any indications of warfarin use were included. In addition, to be included in the quantitative analysis, studies had to report at least one of the outcomes of interest. Exclusion criteria were nonrandomized designs, pediatric patients, or animal studies.

Data Extraction

Data were extracted by two people (K. D. and S. P. S.) in duplicate using standardized data-extraction tables. We obtained data on study and patient characteristics, genotype(s) tested, dosing algorithm, duration of follow-up, and outcomes, including adverse events.

Definitions and Outcomes

The major outcomes were percentage time in therapeutic range (TTR), major bleeding, time to maintenance dose (TMD), supratherapeutic INR of >4 , thromboembolism, nonmajor bleeding, and all-cause mortality. TTR was the primary outcome, whereas all other outcomes

were secondary. The outcomes were stratified by follow-up duration (≤ 1 month and > 1 month).

Outcome Definitions

Percentage Time in Therapeutic Range: Percentage TTR by linear interpolation method as described by Rosendaal et al.²¹

Time to Maintenance Dose: Time required to reach the dose that results in the patient's INR values within the therapeutic range measured at least 7 days apart²² (presented as mean, median, or hazard ratio [HR]).

Thromboembolism: New diagnosis or progression of thromboembolism (pulmonary embolism, DVT, or embolic stroke) after initiation of warfarin.

Major Bleeding: Any fatal bleeding; intracranial, intraspinal, intra-articular, or pericardial bleeding; or bleeding requiring intervention (transfusion or hospitalization).

Nonmajor Bleeding: Bleeding not meeting the definition of major bleeding, including that requiring cessation of treatment.

All-Cause Mortality: Death from any cause after warfarin initiation.

Statistical Analysis

Continuous variables were pooled as mean difference (MD) with 95% CI. Risk ratio (RR) with 95% CI was used to pool the categorical variables. Crude events from each study were used to compute RR with 95% CI. Summary effect for TMD was computed either as continuous variable (if mean $\pm$ SD was reported) or as time-to-event analysis (if HR was reported). DerSimonian-Laird random-effects model was used for meta-analysis of effect size. $P < .05$ (two-tailed) was considered statistically significant for computed effects. The Begg funnel plot was used to visually examine publication bias at outcome level. We used the

Figure 1 – Flow diagram for study selection.

Jadad scale²³ to assess the quality of studies on the basis of randomization, blinding, and attrition of participants. Study heterogeneity was evaluated with Cochran Q and I^2 statistics with $P < .10$ and $I^2 > 60\%$ considered significant heterogeneity, in which case sensitivity analy-

ses were performed by excluding the studies with Jadad score < 2 . Comprehensive Meta-Analysis (CMA 2.2; Biostat, Inc) and Review Manager (RevMan 5.2, The Cochrane Collaboration) were used for meta-analysis.

Results

Description of Included Studies

Initial search resulted in 251 citations with 18 duplicates. Of the 233 studies reviewed for eligibility, we extracted 54 studies for full-text review. We included a total of 10 studies^{17-19,24-30} in qualitative and quantitative analysis (meta-analysis).

The individual study and patient characteristics are presented in Table 1³¹⁻³⁸ and Table 2, respectively. The duration of follow-up was 2 weeks to 6 months. The majority of the patients were white men, and atrial fibrillation/flutter and VTE were main indications of warfarin use. Dosing algorithm was highly variable.^{24,31-38}

Percentage TTR

All studies but one³⁰ reported on this outcome, and all the studies except one used a standard linear interpolation method between successive INR values to calculate

% TTR.²¹ Hillman et al²⁵ did not report on the method used to calculate this variable. At ≤ 1 month follow-up (Fig 2), GD compared with standard dosing resulted in similar % TTR (39.7% vs 40.2%; MD, -0.5 [-3.15 to 2.1]; $P = .7$; I^2 , 0%). At > 1 month follow-up, GD compared with standard dosing resulted in higher % TTR (59.4% vs 53%; MD, 6.35 [1.76 - 10.95]; $P = .007$; I^2 , 73%). Because of significant heterogeneity at > 1 month follow-up, we performed a sensitivity analysis excluding the study with the lowest Jadad score²⁹ that resulted in higher % TTR (MD, 4.82 [1.66 - 7.97]; $P = .003$; I^2 , 35%) and reduced heterogeneity.

Major Bleeding

A total of eight studies^{18,19,24-29} reported on major bleeding. In three studies, no major bleeding was observed in either arm.^{19,24,28} At ≤ 1 month follow-up, GD showed a trend toward reduction on the risk of major bleeding but did not reach statistical significance

TABLE 1] Baseline Study Characteristics

Study/Year	Total Patients Randomized, No.	Total Patients Analyzed, No.	Total Patients Analyzed by Arm, No.		Genotype(s) Tested	Follow-up Duration, mo	Dosing Algorithm	
			Standard Dosing	GD			Standard Dosing	GD
Anderson et al ¹⁷ /2007	206	200	99	101	CYP2C9*2 and *3 & VKORC1	1 mo for post-ortho, 3 for others	10 mg warfarin normogram of Kovacs et al ³¹	Based on their previous observational study ³²
Kimmel et al ¹⁸ /2013	1,015	955	471	484	CYP2C9*2 and *3 & VKORC1	6	Clinical dose initiation and revision algorithm ^{33,34}	Pharmacogenetic dose initiation and revision algorithm ^{33,34}
Burmester et al ¹⁸ /2011	230	225	112	113	CYP2C9, VKORC1 & CYP4F2	0.5	Marshfield pharmacologic model	Marshfield pharmacogenetic model ³⁵
Pirmohamed et al ¹⁹ /2013	455	437	226	211	CYP2C9*2 and *3 & VKORC1	3	Fixed dose algorithm based on age	Loading dose algorithm ³⁷
Hillman et al ²⁵ /2005	38	38	20	18	CYP2C9	1	5 mg/d in all cases	Model based on interactive database ³⁵
Borgman et al ²⁷ /2012	34	26	13	13	CYP2C9*2 and *3 & VKORC1	3	Warfarin induction algorithm by Kovacs et al ³¹	PerMIT software ³⁶
Jonas et al ²⁶ /2013	109	106	53	53	CYP2C9*2 and *3 & VKORC1	3	Washington University School of Medicine algorithm (only clinical variables)	Washington University School of Medicine algorithm (with genotype)
Caraco et al ²⁹ /2008	191	191	96	95	CYP2C9	1	Algorithm by Ageno et al ³⁸	Algorithm designed by them
Huang et al ²⁴ /2009	142	121	60	61	CYP2C9 and VKORC1	1.6	Standard initiation practice in China (2.5 mg)	Algorithm developed by their group ²⁴
Wang et al ³⁰ /2012	106	106	53	53	CYP2C9 & VKORC1	1.6	Standard initiation practice in China (2.5 mg)	Algorithm by Huang et al ²⁴

GD = genotype-guided dosing; post-ortho = post-orthopedic surgery.

TABLE 2] Patient Characteristics of Individual Studies

Study/Year	Age, y		Men, %		White, %		Black, %		Asian, %		Smoking, %		BSA, m ²		Indications, Standard Dosing/GD, %			
	Standard Dosing	GD	Standard Dosing	GD	Standard Dosing	GD	Standard Dosing	GD	Standard Dosing	GD	Standard Dosing	GD	Standard Dosing	GD	Afib/Flutter	VTE	Post-Ortho	Valve
Anderson et al ^{17/} 2007	58.9	63.2	56.6	49.5	94.9	94.1	...	...	...	...	5.1	6.9	...	...	15/13	28/19	55/65	...
Kimmel et al ^{18/} 2013	57	59	49	53	66	67	27	27	...	...	14	15	2.03	2.01	21/23	60/56	...	...
Burmester et al ^{28/} 2011	69.2	67.4	61	57	100	100	0	0	0	0	...	...	1.98	1.96	49/43	38/38	...	17/21
Pirmohamed et al ^{19/} 2013	67.3	67.6	58.8	65.4	98.6	98.6	0.9	0.9	0.5	0.5	12.6	9.5	2.03	2.03	72.7/72.5	27.3/27.5	0/0	0/0
Hillman et al ^{25/} 2005	70.5	68.8	45	44	100	100	0	0	0	0	17	15	2	2	45/17	15/33	15/17	20/22
Borgman et al ^{27/} 2012	45	59	54	54	85	100	...	0	...	0	...	...	...	...	31/38	38/54	...	...
Jonas et al ^{26/} 2013	55.3	56.4	50	43.6	64.8	80	35.2	20	0	0	13	9.1	2.04	1.98	26/42	57/47	...	0/4
Caraco et al ^{29/} 2008	59.7	57.6	43	48	100	100	0	0	0	0	19	21	...	...	31/37	69/63	0/0	0/0
Huang et al ^{24/} 2009	41.6	43	30	32.7	0	0	0	0	100	100	...	...	1.45	1.45	...	0/0	0/0	100/100
Wang et al ^{30/} 2012	42.8	41.9	31.3	30	0	0	0	0	100	100	...	...	1.59	1.57	47.1/36	0/0	0/0	100/100

Afib/flutter = atrial fibrillation/flutter; BSA = body surface area. See Table 1 legend for expansion of other abbreviations.

Figure 2 – Forest plot for percentage time in therapeutic range. df = degrees of freedom; IV = inverse variance.

(RR, 0.46 [0.19-1.11]; $P = .08$; I^2 , 0%). At > 1 month follow-up (Fig 3), GD significantly reduced the risk of major bleeding (0.34 [0.16-0.74]; $P = .006$; I^2 , 0%). GD reduced the absolute risk of major bleeding by around 1.7% (0.9% vs 2.6%).

INR > 4, Nonmajor Bleeding, Thromboembolism, and All-Cause Mortality

A total of seven studies^{18,19,24-28} reported on INR > 4 (e-Fig 1) and eight studies^{17,19,20,23,24,28,30,31} on nonmajor bleeding, thromboembolism, and all-cause mortality (e-Figs 2-4). No thromboembolism was observed in three studies^{24,27,29} and no mortality in four studies.^{24,25,27,29}

At ≤ 1 month follow-up, there was no significant difference in the frequency of patients with supratherapeutic INR > 4 (1.07 [0.87-1.30]; $P = .53$; I^2 , 0%), thromboembolism (1.2 [0.42-3.44]; $P = .74$; I^2 , 0%), nonmajor bleeding (0.96 [0.57-1.62]; $P = .88$; I^2 , 50%), and all-cause mortality (0.97 [0.23-4.02]; $P = .96$; I^2 , 41%). Similarly, at > 1 month follow-up, no difference was seen in these outcomes: supratherapeutic INR > 4.0 (0.90 [0.78-1.04]; $P = .17$; I^2 , 0%), thromboembolism (0.53 [0.21-1.34]; $P = .18$; I^2 , 0%), nonmajor bleeding (0.91 [0.68-1.22]; $P = .52$; I^2 , 39%), and all-cause mortality (0.78 [0.23-2.70]; $P = .70$; I^2 , 41%).

Figure 3 – Forest plot for major bleeding. $M-H$ = Mantel-Haenszel. See Figure 2 legend for expansion of other abbreviation.

Time to Maintenance Dose

Studies reported on TMD as either mean,^{26,29,30} median,^{19,28} or HR.^{18,19,24,29,30} The pooled estimates of HRs (Fig 4) showed that the GD resulted in significantly shorter TMD (HR, 1.79 [1.19-2.70]; $P = .006$; I^2 , 91%). Similarly for estimates by mean, GD resulted in shorter TMD (24.6 days vs 34.1 days; MD, -9.54 days [-18.10 , -0.99]; $P = .029$; I^2 , 92%) (e-Fig 5). Because of significant heterogeneity, we performed sensitivity analysis excluding the study with lowest Jadad score²⁹ and found that GD continued to perform better than standard dosing with new estimates of HR (1.41 [1.13-1.75]; $P = .0000063$; I^2 , 63%) and mean (-6.4 days [-10.4 to -2.4]; $P < .00001$; I^2 , 26%) with reduced heterogeneity.

Study Quality and Publication Bias

Jadad score ranged from 1 to 5. The study by Caraco et al²⁹ had the lowest score (1), and the study by Huang et al²⁴ had the score of 2. Five studies^{19,25,27,28,30} had a score of 3, and three studies^{17,18,26} had a score of 5. No publication bias was observed with visual examination of funnel plot for each outcome that was confirmed by Egger regression intercept and Begg rank correlation.

Discussion

The major findings of this meta-analysis on GD compared with standard dosing of warfarin were similar % TTR at ≤ 1 month and higher % TTR at > 1 month follow-up, a trend toward lower risk of major bleeding at ≤ 1 month and significantly lower risks of major bleeding at > 1 -month follow-up, and shorter TMD. However, the risks of INR > 4.0 , nonmajor bleeding,

thromboembolism, and all-cause mortality were similar between GD vs standard dosing strategies. The efficacy and safety of GD over standard dosing became significant after a month of follow-up.

A prior meta-analysis of GD vs standard dosing of warfarin with three studies (a total of 423 patients) showed no difference in risk of major bleeding with wide CI (RR, 0.69; 95% CI, 0.16-2.9) and a trend toward shorter time to stable dose with GD.³⁹ The current guidelines of the American College of Chest Physicians (CHEST) recommend against genotype testing for warfarin initiation on the basis of data from four RCTs and a meta-analysis with three RCTs.⁴⁰ The present meta-analysis includes 10 RCTs with 2,505 total patients and is consistent with a small but significant difference with GD either having no effect or improving dosing. The findings of the current meta-analysis are in agreement with a prior non-randomized comparative study with 3,584 total patients that showed reduced rates of hospitalization due to bleeding or thromboembolism (6.0% vs 8.1%, $P = .039$) with genotype guidance compared with standard therapy.⁴¹ The patients in that study were followed up for a period of 6 months, during which the difference persisted.

The % TTR is a surrogate of therapeutic warfarin anticoagulation and predictive of thromboembolic⁴² and bleeding complications.³ Patients with higher TTR tend to have fewer thromboembolic and major bleeding events.⁴³ Higher % TTR in the current meta-analysis translated into lower risks of major bleeding at > 1 month follow-up (Figs 2, 3). Although the absolute rates of thromboembolic events were lower

Time-to-maintenance dose (Hazard ratio)

Figure 4 – Forest plot for time to maintenance dose by hazard ratio.

with GD compared with standard dosing after 1 month follow-up, it did not reach statistical significance (0.6% vs 1.4%, $P = .18$), which could be because of the small number of total participants and events compared with the trials of novel oral anticoagulants, which recruited several thousand patients to detect a meaningful difference in risks of major bleeding and thromboembolism.^{44,45} Similarly, the lower risk of major bleeding was seen despite similar risk of supratherapeutic INR > 4 with genotype guidance. However, supratherapeutic INR is only one of the several factors in predicting bleeding in patients undergoing oral anticoagulation.⁴⁶

The benefits of GD are expected to occur during initial days of warfarin initiation, but in the current meta-analysis the benefits were only evident after 1 month of follow-up. One possible explanation for that is following.⁴⁷ When prior dosing and INRs are available along with genotypes, the pharmacogenetic model may be more predictive of warfarin dose beyond the initial few weeks.^{47,48} In a previous study, a pharmacogenetic model explained dose variability to 68% at day 7, 75% at day 14, and 77% at day 21, because of increasing contributions from prior doses and INR response.⁴⁷ Because of close monitoring of the enrolled patients in either arm, the overall event rates were small to observe a meaningful difference, although there was a trend toward benefit at early follow-up. The ongoing Genetics Informatics (GIFT) trial of warfarin to prevent DVT may be able to further explore these issues.⁴⁹ GIFT is currently recruiting patients to see if pharmacogenetic model-based dosing of warfarin reduced adverse outcomes of thromboembolism, major bleeding, supratherapeutic INR, and mortality at 4 to 6 weeks of follow-up.

Our meta-analysis has several clinical implications, because despite the presence of newer anticoagulants, warfarin remains the “gold standard” for a number of indications, particularly in patients with mechanical prosthetic heart valves where at least one of the novel oral anticoagulants (dabigatran) is contraindicated because of excessively high rates of thromboembolic and bleeding complications.⁵⁰ In addition, for the newer anticoagulants (ie, factor IIa and factor Xa inhibitors), there is still uncertainty about the long-term safety profile of these agents. There is no head-to-head comparison between GD of warfarin and new oral anticoagulants. Despite no difference in other safety outcomes of interest, because of significant reduction in major bleeding risk by 66%, GD has important safety implication for patients

on warfarin. A prior meta-analysis of 33 studies of warfarin in the treatment of VTE showed an overall major bleeding-related mortality rate of 13.4% and a risk of intracranial bleeding of 1.1 per 100 patient-years. Given the results of this meta-analysis, CHEST should make the recommendation to consider genotyping, as it has improved % TTR and reduced major bleeding, although it did not change thrombotic outcomes or overall mortality. Prior cost-effectiveness analyses showed genotype guidance to be cost-effective compared with standard dosing if it resulted in 5% to 9% higher TTR⁵¹ and 32% lower risk of major bleeding.⁵² The current meta-analysis resulted in about a 6% increase in TTR and 66% reduction in relative risk of major bleeding. Future studies should be directed at confirming the findings from this meta-analysis and ultimately comparing GD to the novel anticoagulants, as appropriate GD may provide a safer and more efficacious alternative to newer drugs when appropriately used.

Study Limitations

The current meta-analysis is not without limitations. Lack of patient-level data, different duration of follow-up among studies, and variations in algorithm of dosing are major limitations. Because of variations in dosing algorithm, it was not possible to ascertain which algorithm worked better compared with others. However, regardless of algorithm, the incorporation of genotypes in dosing algorithms improved % TTR and reduced risk of major bleeding. Nonuniform reporting by studies is another potential limitation. The study by Kimmel et al,¹⁸ which is the largest study in the meta-analysis, contributed almost 40% to 50% of patients. Despite all these limitations, the current meta-analysis is strengthened by inclusion of studies that were randomized trials, and there was no detectable heterogeneity in most of the outcomes of interest. We observed significant heterogeneity only on % TTR at > 1 month follow-up and TMD, and after sensitivity analyses we were able to reduce the heterogeneity.

Conclusions

As GD of warfarin is effective in reducing risk of major bleeding and improving % TTR and TMD after 1 month of anticoagulation, clinicians should highly consider genotype testing in patients initiating anticoagulation with warfarin. Larger adequately powered RCTs are needed to confirm the benefits of genotype guidance and explore other safety outcomes.

Acknowledgments

Author contributions: K. D. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis from inception to publication. K. D. and S. P. S. contributed to study concept and design, acquisition, analysis or interpretation of data, statistical analysis, and drafting of the manuscript and E. F., J. L., J. H. M., J. N. U., and S. M. W. contributed to acquisition, analysis, or interpretation of data and critical revision of the manuscript for important intellectual content and provided study supervision.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Dr Fung is the recipient of a research grant from the Hitchcock Foundation. Drs Moore and Williams are supported by the National Institutes of Health [Grant GM103534]. Drs Dahal, Sharma, Lee, and Unterborn have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Additional information: The e-Figures can be found in the Supplemental Materials section of the online article.

References

- Kim MJ, Huang SM, Meyer UA, Rahman A, Lesko LJ. A regulatory science perspective on warfarin therapy: a pharmacogenetic opportunity. *J Clin Pharmacol*. 2009;49(2):138-146.
- Garcia D, Regan S, Crowther M, Hughes RA, Hylek EM. Warfarin maintenance dosing patterns in clinical practice: implications for safer anticoagulation in the elderly population. *Chest*. 2005;127(6):2049-2056.
- Lee A, Crowther M. Practical issues with vitamin K antagonists: elevated INRs, low time-in-therapeutic range, and warfarin failure. *J Thromb Thrombolysis*. 2011;31(3):249-258.
- Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ*. 2004;329(7456):15-19.
- Wang D, Chen H, Momary KM, Cavallari LH, Johnson JA, Sadée W. Regulatory polymorphism in vitamin K epoxide reductase complex subunit 1 (VKORC1) affects gene expression and warfarin dose requirement. *Blood*. 2008;112(4):1013-1021.
- Oldenburg J, Marinova M, Müller-Reible C, Watzka M. The vitamin K cycle. *Vitam Horm*. 2008;78:35-62.
- Stehle S, Kirchheiner J, Lazar A, Fuhr U. Pharmacogenetics of oral anticoagulants: a basis for dose individualization. *Clin Pharmacokinet*. 2008;47(9):565-594.
- Moyer TP, O'Kane DJ, Baudhuin LM, et al. Warfarin sensitivity genotyping: a review of the literature and summary of patient experience. *Mayo Clin Proc*. 2009;84(12):1079-1094.
- Fung E, Patsopoulos NA, Belknap SM, et al. Effect of genetic variants, especially CYP2C9 and VKORC1, on the pharmacology of warfarin [published correction appears in *Semin Thromb Hemost*. 2013;39(1):112]. *Semin Thromb Hemost*. 2012;38(8):893-904.
- Siguret V, Pautas E, Gouin-Thibault I. Warfarin therapy: influence of pharmacogenetic and environmental factors on the anticoagulant response to warfarin. *Vitam Horm*. 2008;78:247-264.
- Lindh JD, Holm L, Andersson ML, Rane A. Influence of CYP2C9 genotype on warfarin dose requirements—a systematic review and meta-analysis. *Eur J Clin Pharmacol*. 2009;65(4):365-375.
- Limdi NA, Wadelius M, Cavallari L, et al; International Warfarin Pharmacogenetics Consortium. Warfarin pharmacogenetics: a single VKORC1 polymorphism is predictive of dose across 3 racial groups. *Blood*. 2010;115(18):3827-3834.
- Cavallari LH, Langaee TY, Momary KM, et al. Genetic and clinical predictors of warfarin dose requirements in African Americans. *Clin Pharmacol Ther*. 2010;87(4):459-464.
- Reitsma PH, van der Heijden JF, Groot AP, Rosendaal FR, Büller HRA. A C1173T dimorphism in the *VKORC1* gene determines coumarin sensitivity and bleeding risk. *PLoS Med*. 2005;2(10):e312.
- Wadelius M, Chen LY, Downes K, et al. Common VKORC1 and GGCX polymorphisms associated with warfarin dose. *Pharmacogenomics J*. 2005;5(4):262-270.
- D'Andrea G, D'Ambrosio RL, Di Perna P, et al. A polymorphism in the *VKORC1* gene is associated with an interindividual variability in the dose-anticoagulant effect of warfarin. *Blood*. 2005;105(2):645-649.
- Anderson JL, Horne BD, Stevens SM, et al; Couma-Gen Investigators. Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. *Circulation*. 2007;116(22):2563-2570.
- Kimmel SE, French B, Kasner SE, et al; COAG Investigators. A pharmacogenetic versus a clinical algorithm for warfarin dosing. *N Engl J Med*. 2013;369(24):2283-2293.
- Pirmohamed M, Burnside G, Eriksson N, et al; EU-PACT Group. A randomized trial of genotype-guided dosing of warfarin. *N Engl J Med*. 2013;369(24):2294-2303.
- Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.
- Rosendaal FR, Cannegieter SC, van der Meer FJM, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost*. 1993;69(3):236-239.
- Voora D, Eby C, Linder MW, et al. Prospective dosing of warfarin based on cytochrome P-450 2C9 genotype. *Thromb Haemost*. 2005;93(4):700-705.
- Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17(1):1-12.
- 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(3):226-234.
- 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(3):137-145.
- 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(13):1593-1603.
- 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(3):561-569.
- Burmester JK, Berg RL, Yale SH, et al. A randomized controlled trial of genotype-based Coumadin initiation. *Genet Med*. 2011;13(6):509-518.
- 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 Ther*. 2008;83(3):460-470.
- 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. *Int J Med Sci*. 2012;9(6):472-479.
- 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(9):714-719.
- Carlquist JF, Horne BD, Muhlestein JB, et al. Genotypes of the cytochrome p450 isoform, CYP2C9, and the vitamin K epoxide reductase complex subunit 1 conjointly determine stable warfarin dose: a prospective study. *J Thromb Thrombolysis*. 2006;22(3):191-197.
- Gage BF, Eby C, Johnson JA, et al. Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. *Clin Pharmacol Ther*. 2008;84(3):326-331.
- Lenzini P, Wadelius M, Kimmel S, et al. Integration of genetic, clinical, and INR data to refine warfarin dosing. *Clin Pharmacol Ther*. 2010;87(5):572-578.
- Hillman MA, Wilke RA, Caldwell MD, Berg RL, Glurich I, Burmester JK. Relative impact of covariates in prescribing warfarin according to

- CYP2C9 genotype. *Pharmacogenetics*. 2004;14(8):539-547.
36. Linder MW, Looney S, Adams JE III, et al. Warfarin dose adjustments based on CYP2C9 genetic polymorphisms. *J Thromb Thrombolysis*. 2002;14(3):227-232.
  37. Avery PJ, Jorgensen A, Hamberg AK, Wadelius M, Pirmohamed M, Kamali F; EU-PACT Study Group. A proposal for an individualized pharmacogenetics-based warfarin initiation dose regimen for patients commencing anticoagulation therapy. *Clin Pharmacol Ther*. 2011;90(5):701-706.
  38. Ageno W, Johnson J, Nowacki B, Turpie AGG. A computer generated induction system for hospitalized patients starting on oral anticoagulant therapy. *Thromb Haemost*. 2000;83(6):849-852.
  39. Kangelaris KN, Bent S, Nussbaum RL, Garcia DA, Tice JA. Genetic testing before anticoagulation? A systematic review of pharmacogenetic dosing of warfarin. *J Gen Intern Med*. 2009;24(5):656-664.
  40. Holbrook A, Schulman S, Witt DM, et al; American College of Chest Physicians. Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2_suppl):e152S-e184S.
  41. 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(25):2804-2812.
  42. Connolly SJ, Pogue J, Eikelboom J, et al; ACTIVE W Investigators. 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(20):2029-2037.
  43. Wan Y, Heneghan C, Perera R, et al. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. *Circ Cardiovasc Qual Outcomes*. 2008;1(2):84-91.
  44. Granger CB, Alexander JH, McMurray JJ, et al; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-992.
  45. Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-1151.
  46. Pisters R, Lane DA, Nieuwlaar R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138(5):1093-1100.
  47. Ferder NS, Eby CS, Deych E, et al. Ability of VKORC1 and CYP2C9 to predict therapeutic warfarin dose during the initial weeks of therapy. *J Thromb Haemost*. 2010;8(1):95-100.
  48. Horne BD, Lenzini PA, Wadelius M, et al. Pharmacogenetic warfarin dose refinements remain significantly influenced by genetic factors after one week of therapy. *Thromb Haemost*. 2012;107(2):232-240.
  49. Do EJ, Lenzini P, Eby CS, et al. Genetics informatics trial (GIFT) of warfarin to prevent deep vein thrombosis (DVT): rationale and study design. *Pharmacogenomics J*. 2012;12(5):417-424.
  50. Eikelboom JW, Connolly SJ, Brueckmann M, et al; RE-ALIGN Investigators. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med*. 2013;369(13):1206-1214.
  51. Patrick AR, Avorn J, Choudhry NK. Cost-effectiveness of genotype-guided warfarin dosing for patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2009;2(5):429-436.
  52. Eckman MH, Rosand J, Greenberg SM, Gage BF. Cost-effectiveness of using pharmacogenetic information in warfarin dosing for patients with nonvalvular atrial fibrillation. *Ann Intern Med*. 2009;150(2):73-83.