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Effect of Low-Intensity vs Standard-Intensity Warfarin Prophylaxis on Venous Thromboembolism or Death Among Patients Undergoing Hip or Knee Arthroplasty
A Randomized Clinical Trial

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IMPORTANCE The optimal international normalized ratio (INR) to prevent venous thromboembolism (VTE) in warfarin-treated patients with recent arthroplasty is unknown.

OBJECTIVE To determine the safety and efficacy of a target INR of 1.8 vs 2.5 for VTE prophylaxis after orthopedic surgery.

DESIGN, SETTING, AND PARTICIPANTS The randomized Genetic Informatics Trial (GIFT) of Warfarin to Prevent Deep Vein Thrombosis enrolled 1650 patients aged 65 years or older initiating warfarin for elective hip or knee arthroplasty at 6 US medical centers. Enrollment began in April 2011 and follow-up concluded in October 2016.

INTERVENTIONS In a 2 × 2 factorial design, participants were randomized to a target INR of 1.8 (n = 823) or 2.5 (n = 827) and to either genotype-guided or clinically guided warfarin dosing. For the first 11 days of therapy, open-label warfarin dosing was guided by a web application.

MAIN OUTCOMES AND MEASURES The primary outcome was the composite of VTE (within 60 days) or death (within 30 days). Participants underwent screening duplex ultrasound postoperatively. The hypothesis was that an INR target of 1.8 would be noninferior to an INR target of 2.5, using a noninferiority margin of 3% for the absolute risk of VTE. Secondary end points were bleeding and INR values of 4 or more.

RESULTS Among 1650 patients who were randomized (mean age, 72.1 years; 1049 women [63.6%]; 1502 white [91.0%]), 1597 (96.8%) received at least 1 dose of warfarin and were included in the primary analysis. The rate of the primary composite outcome of VTE or death was 5.1% (41 of 804) in the low-intensity-warfarin group (INR target, 1.8) vs 3.8% (30 of 793) in the standard-treatment-warfarin group (INR target, 2.5), for a difference of 1.3% (1-sided 95% CI, −∞ to 3.05%, P = .06 for noninferiority). Major bleeding occurred in 0.4% of patients in the low-intensity group and 0.9% of patients in the standard-intensity group, for a difference of −0.5% (95% CI, −1.6% to 0.4%). The INR values of 4 or more occurred in 4.5% of patients in the low-intensity group and 12.2% of the standard-intensity group, for a difference of −7.8% (95% CI, −10.5% to −5.1%).

CONCLUSIONS AND RELEVANCE Among older patients undergoing hip or knee arthroplasty and receiving warfarin prophylaxis, an international normalized ratio goal of 1.8 compared with 2.5 did not meet the criterion for noninferiority for risk of the composite outcome of VTE or death. However, the trial may have been underpowered to meet this criterion and further research may be warranted.

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Supplemental content

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Based on data from 58 US emergency departments during the years 2013 and 2014, warfarin accounted for more medication-related emergency visits among older patients than any other drug.[1] However, direct oral anticoagulants, with their rapid onset of action, also cause hemorrhage requiring emergency care,[1] especially after orthopedic surgery.[2-4] Thus, warfarin continues to be prescribed after hip and knee arthroplasty, particularly among high-risk orthopedic patients.[5]

The risk of hemorrhage rises exponentially with international normalized ratio (INR) values higher than 3 or 4.[6-8] Although lower INR values may reduce the risk of hemorrhage, they may provide less protection from thrombosis.[8,9] Among patients with a prior venous thromboembolism (VTE), a target INR value from 1.5 to 2.0 prevented 64% of VTE recurrence compared with placebo,[10] but it is unknown whether a similarly low INR target is safe and effective after arthroplasty.

The American Academy of Orthopedic Surgeons 2007 guideline recommended a target INR of less than 2.0 for patients prescribed warfarin after arthroplasty.[11] A subsequent survey found that US orthopedic surgeons prescribed warfarin more commonly than low-molecular-weight heparin after arthroplasty, and they usually targeted an INR of 2.0 or less.[12] In contrast, other guidelines recommend a target INR of 2.5 (range, 2-3) or do not endorse a specific INR goal after arthroplasty.[13,14] To our knowledge, no multicenter trial has compared low-intensity warfarin to a standard target of 2.5 in patients undergoing orthopedic surgery, and observational studies of INR values 2 or less in patients undergoing arthroplasty have produced conflicting results.[14,15] To address this issue, older patients undergoing arthroplasty were randomized to low-intensity vs standard-intensity warfarin. The trial tested the hypothesis that low-intensity warfarin would be noninferior to standard therapy at preventing the composite outcome of VTE or death.

Key Points

Question Compared with standard intensity warfarin (international normalized ratio [INR] target, 2.5), is a target INR of 1.8 noninferior for preventing the composite outcome of venous thromboembolism (VTE) or death after elective arthroplasty?

Findings In this randomized clinical trial that included 1597 patients aged 65 years or older undergoing hip or knee arthroplasty and receiving prophylactic warfarin, an INR goal of 1.8 compared with 2.5 resulted in a rate of VTE or death of 5.1% vs 3.8%, respectively. The upper confidence limit for the difference (3.05%) exceeded the noninferiority margin of 3.0%.

Meaning Compared with a standard INR goal, a low-intensity INR goal did not meet the noninferiority criterion for risk of the composite outcome of VTE or death among patients undergoing knee or hip arthroplasty; however, the study may have been underpowered to establish noninferiority.

Methods

Trial Design

The Genetic Informatics Trial (GIFT) of Warfarin to Prevent Deep Vein Thrombosis (DVT) was a multicenter randomized clinical trial involving patients initiating warfarin at the time of elective hip or knee arthroplasty. As previously described,[16] we used a 2 × 2 factorial design to randomize participants to (1) genotype-guided vs clinically-guided dosing of warfarin and (2) a target INR of 1.8 vs 2.5. The full protocol is provided in Supplement 1. The protocol was approved by the institutional review board at each site, the US Food and Drug Administration, and the Centers for Medicare & Medicaid Services (CMS). All participants provided written informed consent, and the trial was executed in accordance with the Declaration of Helsinki.

The hypothesis was that low-intensity warfarin (target INR, 1.8) would be non-inferior to standard warfarin (target INR, 2.5) at preventing the composite outcome of VTE or death. Participants were randomized to low- vs standard-intensity warfarin in a 1:1 fashion stratified by site, type of arthroplasty (knee or hip), and self-identified race (black vs other) using blocks of 8. Information on race was collected as required by the National Institutes of Health. The randomization sequence was generated by the webmaster at IsoDynamic.com and could not be predicted by the enrolling providers. The target INR and warfarin doses were open-label.

Trial Participants

Patients planning to undergo elective hip or knee arthroplasty who were 65 years or older and had a life expectancy more than 6 months were recruited. Exclusion criteria included therapeutic warfarin dose known from prior therapy, anticipated nonadherence (ie, patients with known medication nonadherence or alcoholism were excluded because they would be less likely to complete the trial), contraindication to warfarin, a plan to receive an anticoagulant other than warfarin, known thrombophilia, a bleeding disorder, a serious bleed in the past 2 years (unless caused by trauma), baseline INR of 1.35 or more, or an additional indication for warfarin (eg, atrial fibrillation).

Trial Procedures

Warfarin was initiated per institutional protocol: either the night prior to arthroplasty (Washington University in St Louis, University of Utah, and University of Texas Southwestern) or the night of the arthroplasty (Hospital for Special Surgery in New York, Intermountain Healthcare, Salt Lake City, Utah, and Rush University Medical Center, Chicago, Illinois). Dosing of warfarin on days 1 through 11 was accomplished using a web application (http://www.WarfarinDosing.org, investigational device exemption G100317), that incorporated a suite of dosing algorithms to recommend the dose of warfarin after each INR measurement.[17-20] If a prescribed dose differed from the web application by 1 mg/d or more (for doses >3 mg/d) or at least 0.5 mg (for doses ≤3.0 mg/d), it was classified as a *dose deviation*. After day 11 of therapy, clinicians were free to continue the current warfarin dose or change it, depending on subsequent INRs. The INR testing was performed in accordance with standard practice. Groups were treated identically except for randomization to target INR and randomization to either genetic or clinical dosing algorithms.[16] Patients were followed up for 90 days.

Outcomes

Primary Outcome

The primary outcome was the composite of a VTE (confirmed by objective testing) within 60 days, or death within 30 days of arthroplasty. Patients who did not have a symptomatic VTE underwent full lower-extremity duplex ultrasound screening for DVT at approximately 1 month after their arthroplasty.

Secondary Outcomes

Secondary outcomes were INR control and bleeding within 30 days. The percent of time that INR values were in the therapeutic range was calculated using linear interpolation.[21] *Major bleeding* was defined as bleeding into a critical area (intracranial, epidural, intraocular, pericardial, retroperitoneal) or any overt bleeding that resulted in death, a hematoma requiring return to the operating room, a fall in hemoglobin level of 2 g/dL or more, a transfusion of 2 or more units of blood, or hemodynamic changes requiring transfusion (of any number of units of blood). *Nonmajor bleeding* was classified as *clinically relevant* per the protocol and included bleeding that caused any of the following: (1) pain or impairment of activities of daily life; (2) unscheduled contact with a physician; (3) the need for an intervention; (4) an intramuscular hematoma or a subcutaneous hematoma of more than 100 cm^2; (5) epistaxis or spontaneous gingival bleeding lasting for more than 5 minutes; (6) macroscopic hematuria (unless traumatic and <24 hours); and (7) macroscopic gastrointestinal bleeding (except for a few spots on toilet paper) or hemoptysis (except for a few speckles in the sputum).

Other Prespecified Outcomes

Other prespecified outcomes included (1) the composite of VTE (within 60 days) or any of the following events within 30 days of arthroplasty: death, INR of 4 or more, or major bleeding and (2) serious adverse events. Serious adverse events were defined as death, a life-threatening adverse reaction, hospitalization or prolongation of existing hospitalization, a significant incapacity, or medical-surgical intervention to prevent 1 of these outcomes.

Exploratory Outcomes

We prospectively captured cardiovascular and infectious adverse events.

Power Analysis

We selected a sample size of 1600 participants to provide more than 80% power to detect noninferiority. Initially, we assumed a rate of the combined end point (VTE or death) of 16.5%, a 1-sided α of .05, and an absolute margin of inferiority of 5%.[22] An aggregate analysis (with both study groups combined) performed halfway through the trial (after 869 participants were randomized) demonstrated that the mean VTE rate was 5.6%. After an interim analysis that was not prespecified, the data and safety monitoring board recommended reducing the absolute margin of inferiority to 3%. The steering committee accepted this recommendation, noting that an absolute difference of 3% or less in VTE (with most events asymptomatic) would be unlikely to discourage clinicians from using a lower INR goal. This change in the noninferiority margin preserved a study power of more than 80%.

Statistical Analyses

In the primary analysis, participants who received 1 or more doses of warfarin were analyzed in the groups to which they were assigned, regardless of their adherence to study protocol. The secondary analysis was an on-treatment analysis, whereby patients were analyzed based on their target INR, which may have been reassigned for clinical events occurring during follow-up, even if they were initially randomized to a different INR. Statistical analyses were conducted in SAS Analytical Software (SAS Institute Inc) version 9.4 and *R* (version 3.3.1). If 90-day follow-up could not be directly obtained by telephone, the electronic medical record (EMR) was reviewed. Participants who had no follow-up available on or after day 30 were assumed to be alive (no recorded death in EMR). Patients who did not undergo a duplex ultrasound were assumed to be free of DVT (no reported DVT in EMR).

The primary outcome was analyzed by χ^2 test. Secondary analyses of rare events (expected frequency ≤5) were analyzed with the Fisher exact test. The 95% CI for proportions was calculated using the score method incorporating continuity correction, as recommended.[23] Also as recommended,[24] the test of noninferiority was 1 sided. Other tests were 2 sided. We used an α of .05 to determine statistical significance. Because of the potential for type I error due to multiple comparisons, findings for analyses of end points other than the primary end point should be interpreted as exploratory. The homogeneity of treatment effects on the primary outcome across subgroups was examined in a post hoc analysis that tested treatment × subgroup interactions by adding these terms and the subgroups as covariates in a generalized linear model. In a post hoc analysis, we also conducted a mixed-effects model with the stratification variable, site, as a random effect.

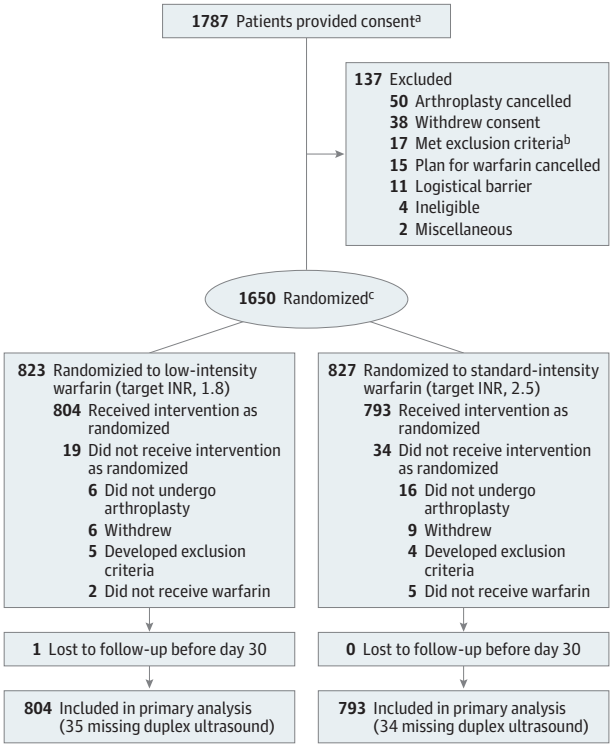
Also in a post hoc analysis, we used logistic regression to check for interactions between the INR intensity and the following variables: genotype vs clinical dosing, sex, race/ethnicity, hip vs knee arthroplasty, age, body mass index (BMI), concomitant antiplatelet therapy use, and $HEMORR_2HAGES$ (hepatic or renal disease, ethanol abuse, malignancy, older age, reduced platelet count or function, rebleeding, hypertension, anemia, genetic factors, excessive fall risk, and stroke) score. When calculating the genetic risk factor, we assigned 1 point to each *CYP2C9*2* variant and 2 points to each *CYP2C9*3* variant.[25]

Results

Flow of the Participants and Their Baseline Characteristics

Enrollment began in April 2011 and follow-up of the final patient was completed in October 2016. Of 1650 randomized patients, 1597 participants received at least 1 warfarin dose after arthroplasty and were included in all analyses. Fifty-three patients were excluded because they did not undergo arthroplasty, withdrew from the trial, never received warfarin, or were found to be ineligible (**Figure 1**). Excluded patients had a higher prevalence of smoking (9.4% vs 3.4%), were more likely to be scheduled for hip arthroplasty (45.3% vs 25.4%), or were more likely to be randomized to standard- rather than to low-intensity warfarin (34 vs 19). A total of 804 participants in the low-intensity warfarin and 793

Figure 1. Consent, Randomization, and Follow-up of Participants



[a] The number of patients screened for eligibility is not known.

[b] A list of the exclusion criteria appears in the Methods section.

[c] Half of participants in each group were simultaneously randomized to clinical vs genetic dosing, as previously detailed.[15]

Table 1. Participant Demographics and Baseline Characteristics

Clinical Variables	No. (%) of Patients	
	Low-Intensity Warfarin (n = 804)[a]	Standard Warfarin (n = 793)
Age, mean (SD), y	72.0 (5.4)	72.1 (5.5)
BMI, mean (SD)	29.0 (5.4)	29.3 (5.6)
Baseline INR, mean (SD)	1.0 (0.1)	1.0 (0.1)
Sex		
Women	513 (63.8)	505 (63.7)
Men	291 (36.2)	288 (36.3)
Indication		
Hip replacement	208 (25.9)	198 (25.0)
Knee replacement	596 (74.1)	595 (75.0)
Dosing algorithm		
Clinical	398 (49.5)	391 (49.3)
Genetic-based	406 (50.5)	402 (50.7)
Race		
White	735 (91.4)	719 (90.7)
Black	47 (5.9)	55 (6.9)
Asian or Indian ancestry	15 (1.9)	14 (1.8)
Alaskan or Native American	0	1 (0.1)
Other	7 (0.9)	4 (0.5)
Ethnicity		
Hispanic	26 (3.2)	16 (2.0)
$HEMORR_2HAGES$ score, mean (SD)[b]	1.39 (1.27)	1.37 (1.21)
Antiplatelet therapy[c]	274 (34.1)	289 (36.4)
Prior major bleed[d]	24 (3.0)	13 (1.6)
History of VTE	6 (0.8)	6 (0.8)
No. of participants per site, median (IQR)[e]	92 (29-327)	91 (29-322)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; $HEMORR_2HAGES$, hepatic or renal disease, ethanol abuse, malignancy, older age, reduced platelet count or function, rebleeding, hypertension, anemia, genetic factors, excessive fall risk, and stroke; INR, international normalized ratio; IQR, interquartile range; VTE, venous thromboembolism.

[a] Low-intensity warfarin used a target international normalized ratio of 1.8 rather than 2.5.

[b] Scores range from 0 to 12, with higher score indicating higher risk of hemorrhage.[25]

[c] Aspirin, cilostazol, dipyridamole, or any thienopyridine.

[d] Includes any self-reported bleed that required transfusion of blood products.

[e] Excludes 1 site that recruited only 1 patient.

in the standard-intensity warfarin received treatment as randomized. The mean age of these 1597 participants was 72.1 years (SD; 5.4 years), 1018 women (63.7%); and 1454 white (91.0%) (**Table 1**). The median days of warfarin therapy was 34 (interquartile range [IQR], 30-36 days]) for both groups. The median number of patients recruited at the 6 sites was 136.5. One patient who was lost to follow-up before the 30-day telephone call was confirmed to have had no pertinent outcomes in the EMR and thus was assumed to be alive and without a VTE.

Protocol Adherence

Of the 17 567 doses recommended by the protocol, 1068 (6%) were dose deviations: 740 in the low-intensity group and 328 in the standard-intensity group (**Figure 2**). In the low-intensity group, 54.5% patients (438) had at least 1 dose deviation; in the standard-intensity group, 27.4% patients (217) had at least 1 dose deviation ($P < .001$). Thirty-five participants (4.4%) in the low-intensity group and 34 (4.2%) in the standard-intensity group did not undergo duplex ultrasound, were asymptomatic, and were assumed to not have a DVT.

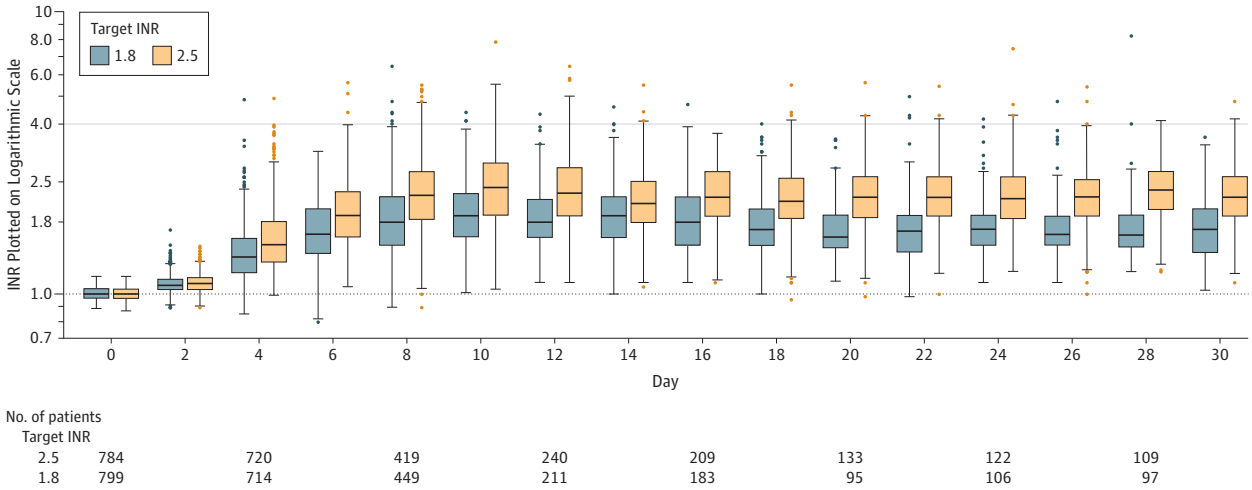
Primary Outcome

The rate of the primary outcome (**Table 2**) was 5.1% (41 of 804) in the low-intensity group and 3.8% (30 of 793) in the standard-intensity group for a difference of 1.3% (1-sided 95% CI, −∞ to 3.05%, $P = .06$ for noninferiority). All of the primary outcomes were VTEs; no patient died. Of the 64 DVTs detected by day 60, 14 were proximal: 8 in the low-intensity group and 6 in the standard-intensity group.

On-Treatment Analysis

Eight patients randomized to the low-intensity group required an increase in target INR postoperatively: 6 due to atrial fibrillation or other arrhythmia, 1 due to a prior VTE, and 1 due to a neurological event. Ten patients randomized to the standard-intensity group had their target INR reduced because of postoperative bleeding (n = 8) or other reasons (n = 2). In an on-treatment analysis (classifying these patients with their new target INR rather than with their randomized INR), the VTE rate was 5.2% (42 of 804) in the low-intensity group and 3.7%

Figure 2. International Normalized Ratio Values Stratified by Target Values



Box plot lines correspond from bottom of box to top: 25th percentile, median percentile, 75th percentile. Whiskers are 1.5 times the interquartile ranges. Circles are extreme values. International normalized ratio (INR) values are shown on a logarithmic scale on even-numbered days of therapy.

Table 2. Components of the Primary and Secondary End Points

End Point	No. (%) of Patients		Absolute Difference (95% CI), %	Relative Risk	*P* Value[a]
	Low-Intensity Warfarin (n = 804)	Standard Warfarin (n = 793)			
VTE (days 1-60) or death (days 1-30)[b]	41 (5.1)	30 (3.8)	1.3 (-∞ to 3.05)	1.35 (-∞ to 2.01)	.06
Death (days 1-30)	0	0			
Asymptomatic DVT	27 (3.4)	22 (2.8)			
Any PE or symptomatic DVT	17 (2.1)	8 (1.0)			
Any PE	8 (1.0)	3 (0.4)			
Major bleed (days 1-30)[c]	3 (0.4)	7 (0.9)	- 0.5 (-1.6 to 0.4)	0.42 (0.11 to 1.62)	.22
Major bleed + INR <4	3 (0.4)	5 (0.6)			
Major bleed + INR ≥4	0	2 (0.3)			
INR ≥4 (days 1-30)	36 (4.5)	97 (12.2)	- 7.8 (-10.5 to -5.1)	0.37 (0.25 to 0.53)	<.001

Abbreviations: DVT, deep vein thrombosis; INR, international normalized ratio; PE, pulmonary embolism; VTE, venous thromboembolism.

[a] This column shows the 1-sided *P* value for noninferiority testing of the primary outcome (VTE or death) and 2-sided superiority *P* values for the secondary outcomes of major bleed and INR of 4 or more.

[b] Primary end point.

[c] Secondary end point. *Major bleeding* was defined as bleeding into a critical area or any overt bleeding that resulted in death, a hematoma requiring return to the operating room, a decrease in hemoglobin level of 2 g/dL or more, a transfusion of 2 or more units of blood, or hemodynamic changes requiring transfusion.

(29 of 793) in the standard-intensity group, for an increase of 1.57% (1-sided 95% CI, −∞ to 3.6%, *P* for noninferiority = .09).

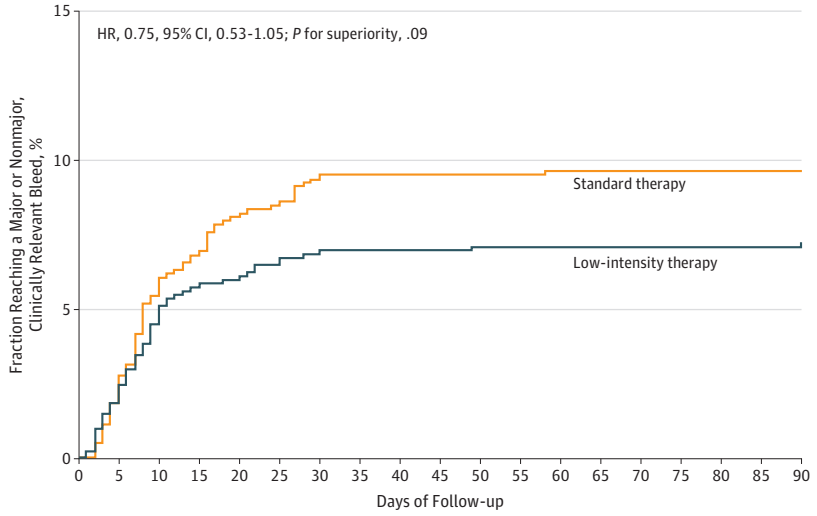
Secondary Outcomes

Among patients in the standard-intensity group, the time in the therapeutic INR range of 2.0 to 3.0 from days 4 through 30 was 53.3%. Among patients in the low-intensity group, the time in the therapeutic range of 1.5 to 2.1 from days 4 through 30 was 52.7%.

Major bleeding within 30 days occurred in 3 patients (0.4%) in the low-intensity group and 7 patients (0.9%) in the standard-intensity group for a difference of −0.5% (95% CI, −1.6% to 0.4%; *P* = .22). For time to major or nonmajor clinically relevant bleeding within 90 days (**Figure 3**), the hazard ratio (HR) was 0.75 (95% CI, 0.53 to 1.05; *P* for superiority = .09) in the low-intensity group, with an absolute difference of −2.4% (95% CI, −5.1% to 0.4%).

International normalized ratio values of 4 or more (**Figure 4**) occurred in 36 patients (4.5%) in the low-intensity group and 97 (12.2%) in the standard-intensity group for an absolute difference of −7.8% (95% CI, −10.5% to −5.1%) and an HR of 0.35 (95% CI, 0.24 to 0.52; *P* < .001). Treatment of the 133 INR values of 4 or more was per standard of care: warfarin was held after 99% (132 of 133) of the high INRs and an INR was repeated within 2 days in 83% (110 of 133) of the high values, with most delays attributed to weekends. Of 133 INR values of 4 or more, there were 2 episodes of major bleeding (both in the standard-intensity group) and 16 nonmajor clinically relevant bleeds.

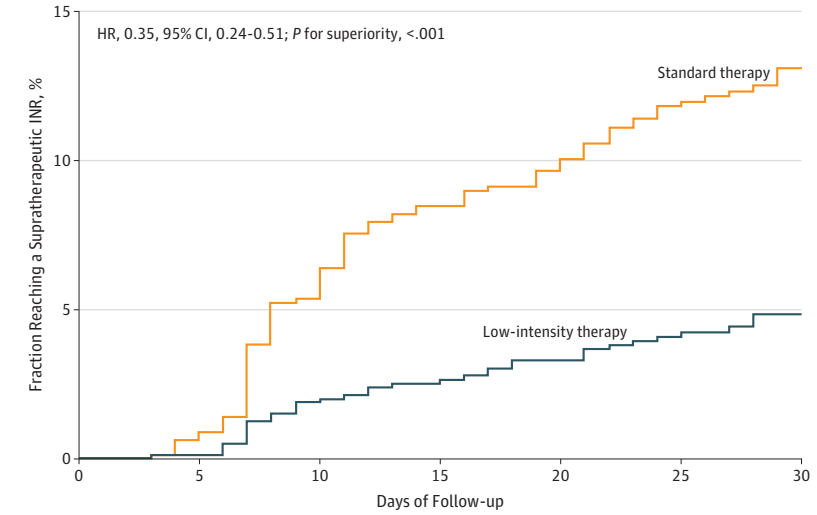
Figure 3. Time to Major or Nonmajor Clinically Relevant Bleed



No. of participants																			
Standard therapy	793	773	742	728	716	711	703	700	700	699	699	699	698	698	696	694	692	688	645
Low-intensity therapy	804	782	759	749	746	739	734	733	733	733	732	731	730	729	728	724	723	722	678

Hazard ratio (HR) based on Cox regression analyses in patients treated with at least 1 dose of warfarin. Median observation time was 90 days (interquartile range [IQR], 90-90) for low-intensity and 90 days (IQR, 90-90) for standard therapy.

Figure 4. Time to Supratherapeutic International Normalized Ratio



No. of participants							
Standard therapy	793	779	734	703	687	566	209
Low-intensity therapy	804	796	773	764	747	620	213

Kaplan-Meier plot of the time to international normalized ratio (INR) value 4 or more among patients treated with at least 1 dose of warfarin. Median observation time was 28 days (interquartile range [IQR], 25-30 days) for low-intensity and 28 days (IQR, 24-30 days) for standard therapy.

Other Prespecified Outcomes

The composite outcome of VTE (within 60 days) or death, major bleeding, or INR of 4 or more within 30 days occurred in 75 patients (9.3%)in the low-intensity group and 128 (16.1%) in the standard-intensity group, for a difference of −6.8% (95% CI, −10.1 to −3.6; $P < .001$) (**Table 3**).

Exploratory Outcomes

There were no significant differences in the rates of cardiovascular or infectious adverse outcomes (post hoc analysis, Table 3).

All tests for interaction (post hoc analysis) were null. Specifically, there was no significant interaction between INR group and any of the following factors: genotype vs clinical dosing, men vs women, black vs white patients (as warfarin dose is influenced by race), hip vs knee arthroplasty, age 65 through 70 years vs age older than 70 years, body mass index, $HEMORR_2HAGES$ score,[25] or concomitant antiplatelet therapy use (**Figure 5**). There was also no significant interaction with either initiation of warfarin preoperatively vs postoperatively ($P = .14$) or with site. In a mixed-effects regression model that included a random term for site, the odds ratio for the primary outcome in the low-intensity group was 1.37 (1-sided 95% CI, −∞ to 2.06, $P = .11$).

Table 3. Adverse Events

Adverse Events (Days 1-30)[a]	No. (%) of Patients	
	Low-Intensity Warfarin (n = 804)	Standard Warfarin (n = 793)
Adverse event, total	121 (15.1)	121 (15.3)
Serious	59 (7.3)	42 (5.3)
Nonserious	72 (9.0)	87 (11.0)
Nonmajor bleed, total[b]	76 (9.5)	89 (11.2)
Clinically relevant bleed	53 (6.6)	68 (8.6)
Other nonmajor bleeds	39 (4.9)	40 (5.0)
Cardiovascular event, total	12 (1.5)	11 (1.4)
Myocardial infarction	3 (0.4)	3 (0.4)
Stroke	1 (0.1)	0
Atrial fibrillation	8 (1.0)	8 (1.0)
Infection by location, total	44 (5.5)	54 (6.8)
Joint infection (hip or knee)	3 (0.4)	3 (0.4)
Wound drainage or cellulitis	19 (2.4)	28 (3.5)
Other infection	25 (3.1)	26 (3.3)

[a] Participants who had multiple adverse events are counted only once in the total rows.

[b] Nonmajor bleeding was classified as clinically relevant per the protocol and included bleeding that caused any of the following: (1) pain or impairment of activities of daily life; (2) unscheduled contact with a physician; (3) the need for an intervention (4) an intramuscular hematoma or a subcutaneous hematoma greater than 100 cm^2; (5) epistaxis or spontaneous gingival bleeding lasting for more than 5 minutes; (6) macroscopic hematuria (unless traumatic and <24 hours); (7) macroscopic gastrointestinal bleeding (except for a few spots on toilet paper), hemoptysis (except for a few speckles in the sputum).

Discussion

In this randomized trial involving older patients undergoing elective hip or knee arthroplasty, the rate of the combined outcome of VTE or death did not meet the prespecified criterion for noninferiority in the low-intensity group compared with the standard-intensity group. Low-intensity warfarin also did not significantly reduce major or nonmajor clinically relevant bleeding compared with standard-intensity warfarin. However, the study may have been underpowered to establish noninferiority.

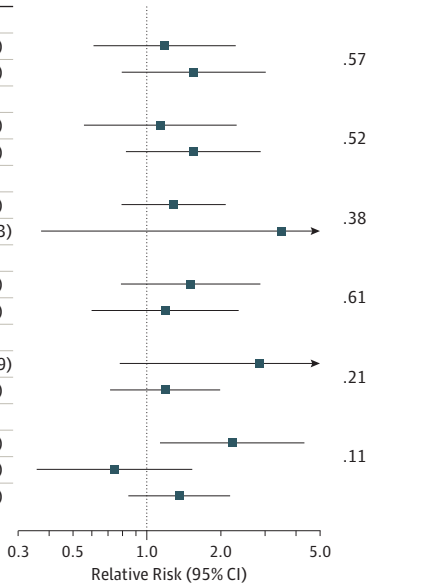
These results are similar to several other studies. For example, the ELATE (Extended Low-Intensity Anticoagulation for Thrombo-Embolism)[9] trial found that after standard VTE treatment, patients randomized to a target INR of 1.5 to 1.9 had significantly more VTE recurrences than those randomized to a target of 2 to 3. Similarly, a prior observational study and a small trial (with only 2 VTEs) found more VTEs after arthroplasty among patients who had an INR persistently of less than 2 compared with patients with higher INR values.[26,27]

Clinical decisions regarding thromboprophylaxis depend on patient-specific risks of thrombosis and hemorrhage, as well as individual preferences.[28,29] Future research could help address which patients at high risk of bleeding might benefit from low-intensity warfarin.

Among patients in the standard-intensity group, the time in the therapeutic range (2.0-3.0) on days 4 through 28 was 53.3%. Among patients in the low-intensity group, the time in the therapeutic range of 1.5 to 2.1 on days 4 through 28 was

Figure 5. Relative Risk of Primary End Point Within Trial Subgroups

Baseline Factor	No. (%) of Patients	No. of Events (%)		Relative Risk (95% CI)	*P* Value for Interaction
		INR 1.8 Group	INR 2.5 Group		
Age, y					
≤70	733 (45.9)	19 (5.2)	16 (4.4)	1.18 (0.62-2.25)	.57
>70	864 (54.1)	22 (5.0)	14 (3.3)	1.54 (0.80-2.97)	
Sex					
Men	579 (36.3)	16 (5.5)	14 (4.9)	1.13 (0.56-2.27)	.52
Women	1018 (63.7)	25 (4.9)	16 (3.2)	1.54 (0.83-2.85)	
Race					
White	1495 (93.6)	38 (5.0)	29 (3.9)	1.28 (0.79-2.05)	.38
Black	102 (6.4)	3 (6.4)	1 (1.8)	3.51 (0.35-32.63)	
Randomization group					
Clinical	789 (49.4)	23 (5.8)	15 (3.8)	1.51 (0.79-2.84)	.61
Genetic	808 (50.6)	18 (4.4)	15 (3.7)	1.19 (0.61-2.32)	
Indication					
Hip	406 (25.4)	9 (4.3)	3 (1.5)	2.86 (0.78-10.39)	.21
Knee	1191 (74.6)	32 (5.4)	27 (4.5)	1.18 (0.72-1.95)	
BMI					
≤30	971 (60.8)	29 (5.7)	12 (2.6)	2.21 (1.14-4.28)	.11
>30	626 (39.2)	12 (4.0)	18 (5.5)	0.74 (0.36-1.51)	
Overall	1597 (100)	41 (5.1)	30 (3.8)	1.35 (0.85-2.14)	



The *P* value is the test for interaction from a logistic regression model. BMI indicates body mass index, calculated as weight in kilograms divided by height in meters squared and INR, international normalized ratio.

52.7%. These levels of INR control were greater than other contemporary trials of genotype-guided warfarin initiation.[30,31] The fraction of patients who developed an INR of 4 or more in both groups was also lower than other trials of warfarin initiation.[30,31] The number of adverse events was low and equal in both groups. This observation differs from observational studies that reported a correlation between postoperative adverse events and high INR values.[32,33]

Two key practices may have enhanced safety in this trial: (1) dosing on days 1 through 11 was accomplished using a web application that used warfarin dosing algorithms,[17-20] although clinicians could deviate from the recommended dose when necessary, and (2) half of the patients in this study were randomized to genotype-guided warfarin dosing.[16]

Strengths of this study include that loss to follow-up was minimal and adherence to both target INR assignment and postoperative duplex ultrasound imaging was good. Treatment groups were balanced demographically and had significantly different INR values, consistent with their assigned group of therapeutic intensity.

Limitations

This study had several limitations. First, the rate of the primary outcome (VTE or death) was lower than anticipated. Thus, the trial may have been underpowered to meet its noninferiority criterion. Second, the trial was open-label. However, the risk of bias was reduced because duplex ultrasound images and imaging tests for pulmonary embolisms were interpreted by physicians who were blinded to study group. Third, participants included a small proportion of minorities. Results may not be generalizable to other more diverse populations.

Conclusions

Among older patients undergoing hip or knee arthroplasty and receiving warfarin prophylaxis, an international normalized ratio goal of 1.8 compared with 2.5 did not meet the criterion for noninferiority for risk of the composite outcome of VTE or death. However, the trial may have been underpowered to meet this criterion, and further research may be warranted.

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