Warfarin Dose Assessment Every 4 Weeks Versus Every 12 Weeks in Patients With Stable International Normalized Ratios
A Randomized Trial
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Background: Guidelines recommend that patients receiving warfarin undergo international normalized ratio (INR) monitoring every 4 weeks.

Objective: To investigate whether assessment of warfarin dosing every 12 weeks is as safe as assessment every 4 weeks.

Design: Noninferiority randomized trial. The randomization schedule (in a 1:1 ratio) was computer-generated, and allocation was concealed until the database was locked by using a centralized schedule. Patients, study and clinical personnel, adjudicators of clinical events, and the study statistician were blinded to treatment assignment. (ClinicalTrials.gov registration number: NCT00356759)

Setting: Single center in Hamilton, Ontario, Canada.

Patients: 250 patients receiving long-term warfarin therapy, whose dose was unchanged for at least 6 months; 226 completed the study.

Intervention: Dosing assessment every 12 weeks (n = 124) compared with every 4 weeks (n = 126) for 12 months. Patients in the 12-week group were tested every 4 weeks; sham INRs within the target range were reported for two of the three 4-week periods.

Measurements: Percentage of time in the therapeutic range (primary outcome) and number of extreme INRs, changes in maintenance dose, major bleeding events, objectively verified thromboembolism, and death (secondary outcomes).

Results: The percentage of time in the therapeutic range was 74.1% (SD, 18.8%) in the 4-week group compared with 71.6% (SD, 20.0%) in the 12-week group (absolute difference, 2.5 percentage points [1-sided 97.5% upper confidence bound, 7.3 percentage points]; noninferiority P = 0.020 for a 7.5-percentage point margin). Fewer patients in the 12-week group than in the 4-week group had any dose changes (37.1% vs. 55.6%; absolute difference, 18.5 percentage points [95% CI, 6.1 to 30.0 percentage points]; P = 0.004). Secondary outcomes did not differ between groups.

Limitations: Patients in the 12-week group had testing and contact with clinic staff every 4 weeks. The study was conducted at a single center and used surrogate outcomes.

Conclusion: Assessment of warfarin dosing every 12 weeks seems to be safe and noninferior to assessment every 4 weeks. A comparison of INR testing, patient contact, and warfarin dose assessment every 12 weeks versus every 4 weeks is necessary before INR testing every 12 weeks can be routinely recommended for practice.

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Anticoagulant treatment with vitamin K antagonists requires frequent prothrombin time (PT) monitoring and dose adjustment (1). Clinical guidelines differ on the optimal interval for PT monitoring. The American College of Chest Physicians recommends a maximum interval of 4 weeks. A 1998 British guideline suggests that PT monitoring can be done up to every 12 weeks for very stable patients (2), but the evidence supporting a longer interval is limited. A retrospective analysis of more than 2000 patients from a British center reported that patients with a stable PT could safely wait 14 weeks between tests (3), whereas an Italian trial comparing PT testing every 4 weeks with every 6 weeks in 124 patients with stable PTs reported no difference in the proportion of patients with extreme INRs (<1.5 and >5) (4) but was underpowered to detect a clinically meaningful difference.

We previously reported that approximately one third of the patients at our large anticoagulation clinic has stable PT results with very infrequent changes in their vitamin K antagonist dose (5). For this population, less frequent PT testing might decrease the burden of anticoagulant therapy. To evaluate the safety and feasibility of such an extended interval, we compared PT testing and dose assessment every 4 weeks versus every 12 weeks over 1 year in patients treated at our clinic with warfarin and whose maintenance dose had been unchanged in the past 6 months.

Methods
Setting and Participants
Study patients were recruited from the anticoagulation clinic at Hamilton Health Sciences-General Hospital in
Prolonged Interval Between INR Tests

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Context
Current guidelines recommend international normalized ratio (INR) monitoring and warfarin dose assessments every 4 weeks.

Contribution
In this trial comparing warfarin dosing assessment every 4 weeks versus every 12 weeks among patients whose warfarin dose had been unchanged for at least 6 months, the proportion of time that patients were within the target INR range did not significantly differ between groups.

Caution
Patients in the group that had dose assessments every 12 weeks had INR testing and supportive contact with clinic staff every 4 weeks.

Implication
Extending the warfarin dosing assessment interval from every 4 to every 12 weeks is probably safe for patients receiving stable doses of warfarin if they continue to have supportive contact with anticoagulation clinic staff every 4 weeks. The findings should not be interpreted to mean that extending INR monitoring to every 12 weeks is proven safe.

—The Editors

Hamilton, Ontario, Canada, which supervised the treatment of 1500 patients at the time of the study. Most of the patients have blood drawn at a decentralized clinic or private laboratory and receive dosing instruction via telephone from our staff. Recruitment began in November 2006 and ended in December 2008. The 12-month visit after the last randomly assigned patient was in December 2009. Written informed consent was obtained from all eligible patients. The local research ethics board at the participating center approved the study.

Patients were eligible for participation if they were receiving long-term warfarin treatment with a therapeutic international normalized ratio (INR) range of 2.0 to 3.0 or 2.5 to 3.5, if they had been managed by our clinic for at least 6 months before enrollment, and if their maintenance dose of warfarin had been unchanged for the previous 6 months or longer. Dose changes on a single day for a deviating INR were permitted. In addition, only patients with PT measured at our hospital laboratory or a local private laboratory, which performs PT analysis for most of our patients (LifeLabs Medical Laboratory Services, Toronto, Ontario, Canada), were enrolled because the study design mandated delayed reporting of extended PT values (see next section) and the consistent ability of the 2 laboratories to return same-day results would minimize any additional delays.

Patients were excluded from the study if they were younger than 18 years, had a life expectancy of less than 1 year, were deemed unsuitable for the study (for example, because of a psychiatric disorder or history of poor adherence), were geographically inaccessible, or did not provide written informed consent.

Randomization and Interventions
A computer-generated randomization list, stratified by INR therapeutic range (2.0 to 3.0 or 2.5 to 3.5) and laboratory (Hamilton Health Sciences-General Hospital or LifeLabs, to control for potential between-laboratory differences), was created by the Ontario Clinical Oncology Group Coordinating and Methods Centre (CMC), located in Hamilton. A binder with the allocation sequences was locked in a drawer in the study coordinator’s office, to which only the coordinator and data management assistant had access. Once consent had been obtained, the investigator, who was also the treating physician, called the CMC to obtain treatment allocation. Patients were assigned in a 1:1 ratio with random block sizes to a warfarin dose assessment schedule of every 4 or every 12 weeks.

Once a patient was randomly assigned, we obtained a medical history, performed a physical examination, and drew blood for a baseline complete blood count and an open-label INR measurement. Appendix Figure 1 (available at www.annals.org) illustrates the study design. All patients were scheduled for PT tests every 4 weeks for 1 year, and INR results were faxed from the laboratory to the CMC. For patients randomly assigned to warfarin dose assessment every 4 weeks, the CMC reported the true INR result to the investigator. Patients randomly assigned to dose assessment every 12 weeks were, in a separate randomization process, randomly allocated to have the first, second, or third true INR result reported to the treating physician consistently throughout the year; the other 2 results were reported as sham values of 1.8 to 3.5 for patients with a therapeutic INR range of 2.0 to 3.0 or 2.0 to 4.0 for patients with a therapeutic INR range of 2.5 to 3.5. The range of sham values outside of the target therapeutic range was intended to promote continuation of stable warfarin dosing on the basis of studies demonstrating that an INR modestly outside the therapeutic range in otherwise stable patients will probably fall within the therapeutic range again by continuing the same warfarin dose.

A physician at the CMC reviewed all true INR results in the 12-week group for extreme values, defined as less than 1.5 or 4.5 or greater. When INR results that were to have been reported as sham values were extreme, the true result was forwarded to the treating physician, as were any follow-up measures (usually 1 week after an extreme INR was found). True INR results were also always reported for measures in association with a clinical event or perioperative management. A manual record of true INRs in both groups was kept at the CMC.

All warfarin dose assessments for the study took place by telephone. We contacted the patients each time they had a PT test, normally every 4 weeks and after any addi-
tional PT tests, to report INR results, assess warfarin dosing, and ask about any bleeding or thromboembolic events or newly started antibiotic treatment. We also routinely reminded patients to report antibiotic treatment, inadequate food intake, plans for surgery or invasive procedures, and changes in their health status.

An end-of-study visit was scheduled for 12 months after randomization and included a history, physical examination, complete blood count, and final PT testing. Patients could withdraw from the trial or be withdrawn at the discretion of the investigator before 12 months if they had major bleeding or thromboembolic events, had repeated extreme INRs, had a change in health status that would affect the stability of the INR, declined to continue participation, or died. Patients whose warfarin therapy was discontinued because of surgery were temporarily removed from the study until their INR was back within the therapeutic range.

All study patients were under active clinical care by the lead author, who saw them at the enrollment visit and the end-of-study visit but made no interim dosing decisions, which were managed and communicated to patients by staff at the anticoagulation clinic. The patients, principal investigator, clinic staff, laboratory staff, and study statistician were blinded to treatment assignment. The study coordinator at the CMC was unblinded to treatment assignment, and the reporting statistician at the data and safety monitoring committee was unblinded at the interim analysis.

**Outcomes and Follow-up**

The primary outcome was the percentage of time in the therapeutic range (TTR), calculated from monthly (and associated) INR results. For each patient, the TTR percentage was calculated by linear interpolation between successive PT test results, and then the number of days in the therapeutic range was estimated (Appendix Figure 2, available at www.annals.org) (8). International normalized ratios between 1.96 and 3.04 (for a target range of 2.0 to 3.0) and between 2.46 and 3.54 (for a target range of 2.5 to 3.5) were considered therapeutic because laboratories reported INRs rounded to 1 decimal (for example, 1.96 was reported as 2.0).

Secondary outcomes were extreme INRs (number of patients as well as number of extreme INRs per patient), changes in the maintenance dose, major bleeding events according to published criteria (9), objectively verified thromboembolic events, and deaths. A blinded central adjudication committee evaluated all clinical events according to predefined criteria.

**Statistical Analysis**

The study was designed to assess the noninferiority of warfarin dosing assessment every 12 weeks versus every 4 weeks. On the basis of a retrospective review performed at our clinic of 51 patients with an unchanged maintenance dose over the previous 6 months, we estimated that the
TTR percentage for stable patients was 77% (SD, 16.5%). From an informal sampling of experts, we judged an absolute difference of 5 to 10 percentage points in TTR percentage as unacceptable (10). We therefore set the noninferiority margin at 7.5 percentage points and hypothesized that an absolute between-group difference (4-week minus 12-week group) less than 7.5 percentage points would constitute noninferiority for every 12-week compared with every 4-week dosing. With a 1-sided $\alpha$ level of 2.5% and a power of 90%, we needed a minimum of 102 patients per group to demonstrate noninferiority. Allowing for 5% loss to follow-up, we planned to enroll 214 patients (107 into each group).

An interim analysis, planned to occur after 100 patients had been in the study for at least 6 months, was performed by the data and safety monitoring committee. A Haybittle–Peto stopping guideline (1-sided $P < 0.001$) was used to assess whether the patients in the experimental group were statistically significantly disadvantaged with regard to TTR percentage and the proportion of patients with at least 1 extreme INR ($<1.5$ or $\geq4.5$). The interim analysis revealed that the variability of TTR percentage was larger than anticipated. On the basis of a blinded reassessment of sample size that considered the revised variance estimate, the data and safety monitoring committee recommended an increase in sample size from 214 to 250 patients.

All analyses included all patients by treatment as randomly assigned. The TTR percentage was calculated from randomization to the point of early withdrawal or end of the study. We did not impute values for missed INRs but used linear interpolation as described in Appendix Figure 2 to calculate TTR percentage between the 2 observed true INR results. We compared the mean TTR percentage in the 2 groups by using 1-sided 2-sample $t$ tests, both unadjusted and adjusted for the strata and offset by the noninferiority margin, to test the null hypothesis of inferiority of the experimental group against the alternative of noninferiority at an $\alpha$ level of 0.025. Linear modeling was used to evaluate the consistency of treatment effects among subgroups by testing for interactions between the treatment group and clinically relevant subgroups (INR therapeutic range, laboratory, sex, use of antiplatelet therapy, heart failure, and diabetes mellitus), and we used general linear modeling to assess the association among baseline clinical factors (age, sex, use of antiplatelet therapy, heart failure, and diabetes mellitus), INR therapeutic range, laboratory, and treatment group on TTR percentage. We used chi-square tests for superiority to compare the proportion of patients in each group who had an extreme INR and those who had a dose change. Data were analyzed by using SAS, version 9.2 (SAS Institute, Cary, North Carolina).

**Role of the Funding Source**

Funding was obtained from the Physicians’ Services Incorporated Foundation. The funding source had no role in the design or conduct of the study, analysis or interpretation of the data, or the decision to submit the manuscript for publication.

**RESULTS**

Between 26 November 2006 and 19 December 2008, we screened 272 potentially eligible patients for inclusion and randomly assigned 250 (Figure 1). Twenty-four patients (9.6%) withdrew from the study early: 14 in the 4-week group (mean days in study, 172 [SD, 95]) and 10 in the 12-week group (mean days in study, 205 [SD, 114]). Reasons for early withdrawal are detailed in Figure 1. Patient characteristics were similar at baseline (Table 1). No temporary interruptions for surgery occurred during the study.

**INR and TTR**

Mean TTR percentage was 74.1% (SD, 18.8%) in the 4-week group and 71.6% (SD, 20.0%) in the 12-week group. The absolute difference of 2.5 percentage points favored the 4-week group with a 1-sided upper 97.5% confidence bound of 7.3 percentage points that was within the noninferiority margin of 7.5 percentage points (unad-

| Table 1. Baseline Characteristics |
|-----------------------------------|
| **Characteristic** | **4-Week Group (n = 126)** | **12-Week Group (n = 124)** |
| **Median age (min, max), y** | 72 (29, 93) | 70 (23, 92) |
| **Median weight (min, max), kg** | 82 (45, 164) | 82 (44, 139) |
| **Median weekly warfarin dose (min, max), mg** | 35 (9, 78) | 32 (9, 100) |
| **Sex, n (%)** | | |
| Men | 87 (69) | 87 (70) |
| Women | 39 (31) | 37 (30) |
| **Laboratory, n (%)** | | |
| LifeLabs | 90 (71) | 88 (71) |
| HHS-General Hospital | 36 (29) | 36 (29) |
| **Indication, n (%)** | | |
| Atrial fibrillation | 73 (58) | 69 (56) |
| Heart valve replacement | 52 (41) | 51 (41) |
| Venous thromboembolism | 18 (14) | 18 (15) |
| Other | 3 (2) | 3 (2) |
| $\geq2$ indications | 20 (16) | 17 (14) |
| **Therapeutic-range INR, n (%)** | | |
| 2.0–3.0 | 111 (88) | 109 (88) |
| 2.5–3.5 | 15 (12) | 15 (12) |
| **Aspirin or clopidogrel, n (%)** | | |
| Yes | 50 (40) | 45 (36) |
| No | 76 (60) | 79 (64) |
| **Medical history, n (%)** | | |
| Stroke | 17 (13) | 24 (19) |
| Pulmonary embolism | 11 (9) | 10 (8) |
| Deep venous thrombosis | 19 (15) | 14 (11) |
| Systemic embolism | 1 (1) | 4 (3) |
| Major bleeding event | 15 (12) | 9 (7) |
| Congestive heart failure | 28 (22) | 38 (31) |
| Diabetes mellitus | 31 (25) | 27 (22) |

HHS = Hamilton Health Sciences; INR = international normalized ratio; max = maximum; min = minimum.
justed \( P = 0.020 \); adjusted \( P = 0.019 \) for tests of noninferiority). The proportion of patients with at least 1 change in maintenance dose during the study and the number of dose changes was greater in the 4-week group, but there were otherwise no differences in secondary outcomes (Table 2). No dose changes in the 12-week group were made in response to sham INR results.

Extreme INRs (≥4.5) occurred in 8 patients in the 12-week group; 6 at the time of scheduled true INR reports and 2 at the time of sham INR reports. Five of the 8 patients had an identifiable cause for the extreme value (temporary high-dose acetaminophen \( [n = 2] \), ciprofloxacin \( [n = 1] \), diuretic \( [n = 1] \), and terminal illness \( [n = 1] \)). Of the 2 patients whose sham values required unblinding, the first patient’s initial INR was 5.6 at week 44, which returned to within range (3.6) at the next measure after 2 warfarin doses were withheld and then the maintenance dose was continued. The other patient had an initial INR of 4.6 at week 48, which returned to within range (2.7) at the next measure after 1 dose of warfarin was withheld and the maintenance dose was decreased by 12.5%.

No statistically significant interactions between treatment group and TTR percentage were found among subgroups defined by INR therapeutic range, laboratory, sex, use of antiplatelet agents, heart failure, or diabetes mellitus (Figure 2).

Factors associated with higher TTR percentage were female sex; INR testing at the Hamilton Health Sciences-General Hospital laboratory; and, with borderline statistical significance, an INR therapeutic range of 2.0 to 3.0. Heart failure was associated with a lower TTR percentage. The other variables (age, treatment, and antiplatelet therapy) were not associated with TTR percentage (Appendix Table, available at www.annals.org).

**Clinical Events**

Five deaths (3 thromboembolic) occurred in the 4-week group (INRs of 2.2, 2.4, and 2.6 before the thromboembolic events and 1.8 and 3.5 before other deaths) and 2 deaths (neither thromboembolic) occurred in the 12-week group (INRs of 2.0 and 2.5 before death). Only 1 thromboembolic event was objectively verified and involved systemic embolism in a patient in the 4-week group whose INR was 6.8 on the same day. In addition, 3 patients in the 4-week group and 2 patients in the 12-week group had events adjudicated as transient ischemic attacks, with same-day INRs between 2.1 and 3.1. Major bleeding events, all nonfatal, were observed in 1 patient in the 4-week group (INR, 2.3) and 2 patients in the 12-week group (INRs, 3.3 and 4.5, respectively), and 11 patients (4 in the 4-week group and 7 in the 12-week group) reported 1 minor bleeding event each.

The mean change in hemoglobin levels from the baseline visit to the end-of-study visit was negligible in both groups.

### Table 2. Characteristics of Warfarin Treatment During the Study

| Outcome | 4-Week Group | 12-Week Group* | Absolute Difference (CI), percentage points | \( P \) Value |
|---------|--------------|---------------|--------------------------------------------|--------------|
| Mean time in study (SD), \( d \) | 349 (72) | 355 (56) | -6.0 (-9.2 to -2.9) | 0.004* |
| Mean PT tests (SD), \( n \) | 11.9 (2.5) | 12.4 (2.3) | -0.5 (-1.5 to 0.5) | 0.43 |
| Mean time in therapeutic range (SD), % | 74.1 (18.8) | 71.6 (20.0) | 2.5 (7.3)† | 0.020‡ |
| Mean number of INRs in therapeutic range (SD) | 8.4 (2.8) | 8.4 (2.9) | 0.00 | 0.99 |
| Patients with extreme INRs, \( n \) %§ | | | | |
| INR ≥4.5 | 15 (11.9) | 8 (6.5) | 7.4 (4.0 to 10.9) | 0.02 |
| INR ≤1.5 | 12 (9.5) | 11 (8.9) | 0.6 (-4.1 to 5.3) | 0.80 |
| Number of extreme INRs, \( n \) % | | | | |
| 0 | 99 (78.6) | 107 (86.3) | 7.7 (-1.8 to 17.1) | 0.11 |
| 1 | 19 (15.1) | 12 (9.7) | 5.2 (-2.8 to 13.1) | 0.22 |
| 2 | 6 (4.8) | 4 (3.2) | 2.6 (-3.2 to 8.4) | 0.41 |
| 3 | 2 (1.6) | 1 (0.8) | 1.8 (-5.0 to 8.6) | 0.63 |
| ≥4 dose changes | 8 (6.3) | 4 (3.2) | 5.1 (-1.8 to 12.0) | 0.15 |
| ≥1 dose change | 70 (55.6) | 46 (37.1) | 24.5 (6.1 to 42.9) | 0.004 |
| Patients with dose changes, \( n \) % | | | | |
| 0 dose changes | 56 (44.4) | 78 (62.9) | -22.5 (-39.1 to -5.9) | 0.003 |
| 1 dose change | 38 (30.2) | 19 (15.3) | 13.0 (-0.4 to 26.4) | 0.05 |
| 2 dose changes | 13 (10.3) | 17 (13.7) | -4.4 (-13.4 to 4.6) | 0.84 |
| 3 dose changes | 11 (8.7) | 6 (4.8) | 6.9 (-1.8 to 15.6) | 0.11 |
| ≥4 dose changes | 8 (6.3) | 4 (3.2) | 5.1 (-1.8 to 12.0) | 0.15 |
| Clinical events, \( n \) % | | | | |
| Major bleeding event | 1 (0.8) | 2 (1.6) | -1.8 (-4.9 to 1.4) | 0.32 |
| Verified thromboembolic event | 1 (0.8) | 0 (0) | 0.8 (-2.3 to 4.4) | 0.32 |
| Death | 5 (4.0) | 2 (1.6) | 2.4 (-2.3 to 7.5) | 0.25 |

INR = international normalized ratio; PT = prothrombin time.
* \( Z \) of every 3 results in this group were shams.
† One-sided 97.5% upper confidence bound (i.e., noninferiority concluded if <7.5%).
‡ Test of inferiority vs. noninferiority (margin, 7.5%); all other \( P \) values refer to superiority tests.
§ Patients may have >1 extreme INR.
|| 2-sided 95% CI.
DISCUSSION

This randomized trial compared dosing assessment every 12 weeks with every 4 weeks for patients receiving a stable dose of warfarin for at least 6 months. Our results suggest that every-12-week dosing is noninferior to every-4-week dosing with respect to the percentage of time spent in the therapeutic INR range and is safe and feasible. More dose changes occurred in the 4-week group, some of which were probably unnecessary and attributable to temporary fluctuations in the INR due to deviations in the diet or short-term use of an interacting drug. In a search of MEDLINE (1966 to 2011), EMBASE (1980 to 2011), and CINAHL (1982 to 2011) using the search terms oral anticoagulants, warfarin, and intervals and applying the “randomized control trial” filter, we identified only 1 similar trial comparing dosing intervals that was underpowered to detect a between-group difference (5). Thus, we believe our study is the first adequately powered trial to evaluate the safety of prolonged intervals between PT tests in stable patients by using the surrogate outcome of TTR percentage.

Our trial had some limitations. It was not a true evaluation of INR monitoring and dosing assessment every 12 weeks, because patients had blood drawn and were contacted by telephone every 4 weeks for sham result reporting and to remind them of important factors for INR instability (use of antibiotics and change in health status). Ongoing contact every 4 weeks could have increased adherence to treatment more than monitoring and contact every 12 weeks. Related, extreme INR results (1.5% of all INRs) in the 12-week group were reported unblinded in a procedure that also deviates from true 12-week testing and dosing because we considered it unethical not to inform the investigator of the extreme results, particularly for high INRs. Only 2 unblinded high INRs were found, which led to subsequent modest dose adjustments.

The trial was not powered to assess differences in clinical outcomes. We designed the study as a phase 2 randomized trial with a surrogate primary outcome because the event rate of important clinical outcomes is low in stable patients with a high TTR percentage (1). We would there-

**Figure 2. Absolute difference between the treatment groups in the percentage of time in the therapeutic range, by subgroup, and interaction between subgroups and treatment group.**

| Characteristic | Absolute Difference in Time in the Therapeutic Range (95% CI), percentage points | P Value for Interaction |
|---------------|-----------------------------------------------------------------------------------|------------------------|
| INR therapeutic range |                                                                                   |                        |
| 2.0–3.0       | 2.50 (–2.62 to 7.62)                                                              | 0.91                   |
| 2.5–3.5       | 1.70 (–12.20 to 15.60)                                                             |                        |
| Laboratory    |                                                                                   |                        |
| LifeLabs      | 2.90 (–3.14 to 8.94)                                                              | 0.75                   |
| Hamilton Health Sciences-General Hospital | 1.20 (–5.90 to 8.30) |                        |
| Sex           |                                                                                   |                        |
| Men           | 3.90 (–2.14 to 9.94)                                                              | 0.36                   |
| Women         | –1.00 (–8.57 to 6.57)                                                             |                        |
| Aspirin or clopidogrel use |                                                                                   |                        |
| Yes           | 4.80 (–2.96 to 12.60)                                                             | 0.47                   |
| No            | 1.10 (–5.11 to 7.31)                                                              |                        |
| Congestive heart failure |                                                                                   |                        |
| Yes           | 1.10 (–8.70 to 10.90)                                                             | 0.88                   |
| No            | 2.00 (–3.49 to 7.49)                                                              |                        |
| Diabetes      |                                                                                   |                        |
| Yes           | 1.60 (–9.57 to 12.80)                                                             | 0.85                   |
| No            | 2.10 (–3.21 to 7.41)                                                              |                        |

INR = international normalized ratio.
fore need several thousand patients to demonstrate non-inferiority for clinical outcomes; before embarking on such a large trial, we believed that obtaining preliminary proof of safety was important. In an attempt to translate TTR percentage to a clinical outcome, van Walraven and colleagues (10) used a model with Monte Carlo simulations and association measures and concluded that an increase in TTR percentage of 8.4% could be translated to a non–statistically significant decrease of 0.66% per year in bleeding and thromboembolic events. The observed difference in TTR percentage between groups in our study was 2.5 percentage points, which would not be expected to translate into a difference in clinically important outcomes.

Finally, the generalizability of our findings may be limited because the trial was conducted at a single center. The results may not be applicable in countries where vitamin K antagonists with shorter half-lives (such as acenocoumarol) are predominantly used.

Nevertheless, we believe that these trial findings have potential implications for practice. Newer oral anticoagu-

lants, whose actions are so predictable that laboratory monitoring is not necessary (11), may advance a standard of less frequent monitoring even among patients taking warfarin, some of whom may have modest interest in switching to newer agents that are much more costly. Most patients would appreciate the prospect of less frequent visits to the laboratory for INR monitoring. The total cost of warfarin treatment—including indirect costs—is much greater than the cost of the drug itself because of the need for monitoring and dose adjustment (12). If our local experience that one third of patients receiving warfarin has stable doses and INR results can be generalized to the millions of people in the United States currently receiving long-term warfarin therapy (13), using prolonged test intervals may result in substantial savings.

In summary, in a comparison of every-12-week to every-4-week dosing assessment for patients receiving a stable dose of warfarin for at least 6 months, every-12-week dosing was noninferior to every-4-week dosing with respect to the percentage of time spent in the therapeutic INR range, and the prolonged dosing assessment interval seemed safe. Because patients assigned to 12-week assessment had 4-week INR monitoring and contact with anti-coagulation staff, a phase 3 trial comparing testing and contact every 4 weeks with every 12 weeks would be necessary before prolonged intervals for testing and dose assessment can be recommended for clinical practice.

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Appendix Figure 1. Presentation of true and sham international normalized ratios to the treating physician, by treatment group.

R = randomization.
Appendix Figure 2. Description of TTR calculation.

The raw data consist of a series of k INR and data pairs \((\text{INR}_i, T_i)\) for each patient observed during the study period, and the fixed upper and lower limits of the acceptable INR therapeutic range \((\text{INR}_U, \text{INR}_L)\). In the example below, there are \(k = 7\) assessment dates (from \(T_7\) to \(T_1\)) with INR levels (from \(\text{INR}_1\) to \(\text{INR}_7\)) that demonstrate the most common situations (labeled A, B, C, D, E, F, G).

The TTR can be calculated easily if one assumes that the “instantaneous” unobserved INRs between observation times follow a linear path (i.e., “you join the dots”). Therefore, the table below summarizes the number of days that the patient remained within and outside of (either below or above) the therapeutic range, depending on the location of the segments relative to the INR boundaries.

| Segment | Days in Therapeutic Range | Days out of Therapeutic Range |
|---------|---------------------------|-------------------------------|
|         | (1)                       | (2)                          | (3)                          | (4)                          |
| AB      | 0                         | \(T_2 - T_1\)                | 0                            | 0                            |
| BC      | \(T_3 - TL_1\)            | \(TL_1 - T_2\)               | 0                            | 0                            |
| CD      | \(T_4 - T_3\)             | 0                            | \(T_5 - TU_1\)               | 0                            |
| DE      | \(T_{U_1} - T_4\)         | 0                            | \(T_6 - T_{U_2}\)            | \(T_7 - T_5\)                |
| EF      | 0                         | 0                            | \(T_6 - T_5\)                | \(T_7 - T_5\)                |
| FG      | \(TL_2 - T_{U_2}\)        | \(T_7 - TL_2\)               | \(TU_2 - T_6\)               | \(TU_2 - T_6\)               |

The only unknowns in this table are the \(TL\) and \(TU\) times for segments that cross the lower or upper INR therapeutic range boundaries (BC, DE, and FG). These can be calculated through interpolation as follows:

For positive slope segments (i.e., \(\text{INR}_{i+1} > \text{INR}_i\)): 

\[
TX = T_i + \left(\frac{\text{INR}_i - \text{INR}_{i+1}}{\text{INR}_{i+1} - \text{INR}_i}\right) (T_{i+1} - T_i)
\]

For negative slope segments (i.e., \(\text{INR}_{i+1} < \text{INR}_i\)): 

\[
TX = T_i + \left(\frac{\text{INR}_i - \text{INR}_{i+1}}{\text{INR}_i - \text{INR}_{i+1}}\right) (T_{i+1} - T_i)
\]

where \(X = U\) for upper or \(L\) for lower boundaries, \(i\) represents the sequence number of the observed time immediately prior to the point where the boundary is crossed, and \(i + 1\) is the next observed time in the sequence.

Values falling on the boundaries are considered to be within the therapeutic range. One additional refinement was made to the algorithm to allow a small tolerance at the INR limits (e.g., 0.05 added to the upper limit and 0.05 subtracted from the lower limit to account for overcalling out-of-range INRs due to the assumption that INRs rise and fall along a precise continuum and because the laboratories reported INR values to only 1 decimal place).

Finally, the TTR is simply the sum of column 2 in the table above and is expressed as a percentage of the total time on study, \(T_k - T_1\). Similar calculations can be performed for the time above the upper therapeutic range boundary (column 4) and time below the lower limit (column 3).

\(\text{INR} = \) international normalized ratio; \(\text{TTR} = \) time in therapeutic range.
## Appendix Table. Predictors of Higher Percentage of Time in Therapeutic Range, Based on a General Linear Model

| Variable                                           | Estimate (95% CI), percentage points* | P Value |
|----------------------------------------------------|----------------------------------------|---------|
| Dose assessment: 4-wk vs. 12-wk                    | 1.7 (–3.0 to 6.5)                      | 0.48    |
| Therapeutic range INR: 2.0 to 3.0 vs. 2.5 to 3.5   | 7.4 (–0.1 to 15.0)                     | 0.052   |
| Laboratory: HHS-General Hospital vs. LifeLabs      | 6.1 (0.7 to 11.5)                      | 0.024   |
| Sex: women vs. men                                 | 6.7 (1.4 to 12.1)                      | 0.014   |
| Antiplatelet therapy: yes vs. no                   | 2.4 (–2.6 to 7.5)                      | 0.34    |
| Age (per 10 y)                                     | –0.5 (–2.4 to 1.5)                     | 0.61    |
| Congestive heart failure: yes vs. no               | –6.9 (–12.3 to –1.4)                   | 0.014   |
| Diabetes mellitus: yes vs. no                      | 0.7 (–5.0 to 6.5)                      | 0.80    |

HHS = Hamilton Health Sciences; INR = international normalized ratio.
* Estimate is the absolute increase or decrease in percentage of time in the therapeutic range.