Warfarin: Optimising Time in Therapeutic Range (TTR)

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Thromboembolism is a major cause of morbidity and mortality worldwide.
Focus of presentation is warfarin in people with Atrial Fibrillation

• Long term use
• Multiple concomitant medications
• Polymorbidity
• Increasing incidence and prevalence

• The most common anticoagulant used for stroke risk reduction in people with AF is warfarin

• Warfarin has been shown in over 20 RCTs to reduce risk of stroke in AF patients by approximately 65%

• Warfarin was developed in 1948 by Paul Link at the University of Wisconsin for use as a rodent poison which resulted in the acronym WARF, for Wisconsin Alumni Research Fund + the ending -arin for coumarin

• Warfarin needs to be closely monitored using INR testing to ensure appropriate level of anticoagulant control and bleeding risk

• Its response is variable within and between individuals
Frequency distribution of warfarin daily dose requirement
Pharmacogenomics. 2009, 10 (12) :1955-1965

Mean dose = 4.42 ± 2.40 mg,
(95% CI: 4.36–4.49 mg)

n = 5701

INR target for non-valvular atrial fibrillation

Adjusted odds ratios for ischemic stroke and intracranial bleeding in relation to intensity of anticoagulation.
• Coagulation monitoring using INR has formed the cornerstone to the effective management of patients receiving warfarin.

• It is required to compensate for the complex pharmacokinetics of warfarin, especially the high inter- and intrapatient variability and multiple food and drug interactions that leads to the need for dose adjustment.

Schematic diagram of the action of warfarin
Warfarin is administered as a racemic mixture of S and R enantiomers. Cytochrome P450 2C9 inactivates the more potent S-warfarin enantiomer. Warfarin inhibits vitamin K epoxide reductase, preventing recycling of vitamin K leading to partially carboxylated sub-or non-functional coagulation proteins.
The main sources of variability for warfarin response may be anticipated to relate to the following:

- body weight
- diet (Vit K supply, inhibitors/inducers of CYP enzymes)
- smoking
- genetics of CYP enzymes
  - particularly CYP2C9 for S-warfarin, but also other CYP enzymes involved with R warfarin.
- genetics of breakdown of Vit K and the epoxide reductase complex
- drug interaction with CYP enzymes

Consensus guidelines for warfarin therapy
Alex S Gallus, Ross I Baker, Beng H Chong and Paul A Ockelford

"Warfarin presents a very good case study with respect to drug response variability, and the management of the uncertainty that surrounds the therapeutic use of warfarin"
Warfarin inhibits the reductase that recycles warfarin epoxide (Vit K epoxide reductase C1) so that it can be used again in the production of the Vit K dependent clotting factors.

Warfarin is optically active, and the two isomers, R and S warfarin, have different potencies and pharmacokinetic characteristics.

The S warfarin has 5 times the potency of R warfarin and so often has been taken to represent the active ingredient of racemic warfarin. This is a convenient over-simplification, but not all warfarin activity is accounted for by only the S isomer.

This is further complicated by the fact that the isomers are metabolized preferentially by different CYP450 enzymes and have different elimination half-lives. S warfarin has a long half-life - an average of 40 hours. In some individuals it may be up to or longer than 60 hours.

After initiation of dosing, S warfarin doesn't achieve steady-state concentrations until about a week of dosing.

However the anticoagulant effects are not only dependent on warfarin kinetics but also on the kinetics of the clotting factors, which have their own half lives of elimination.

This means that after warfarin steady-state is reached, some more time is required for the clotting factors, and consequently the fully anticoagulant effect, to settle into 'steady-state'. Simulations suggest that the whole process of anticoagulation may take up to about 2 weeks to reach steady-state.

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Adelaide Stroke Incidence Study
Declining Stroke Rates but Many Preventable Cardioembolic Strokes

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Background and Purpose—Stroke incidence rates are in flux worldwide because of evolving risk factor prevalence, risk factor control, and population aging. Adelaide Stroke Incidence Study was performed to determine the incidence of strokes and stroke subtypes in a relatively elderly population of 138 000 people in the Western suburbs of Adelaide.

Methods—All suspected strokes were identified and assessed in a 12-month period from 2009 to 2010. Standard definitions for stroke and stroke fatality were used. Ischemic stroke pathogenesis was classified by the Trial of ORG 10172 in Acute Stroke Treatment criteria.

Results—There were 318 stroke events recorded in 301 individuals; 238 (75%) were first-in-lifetime events. Cerebrovascular accident incidence rates for first-ever strokes were 161 per 100 000 per year overall (95% confidence interval [CI], 141-183), 176 for men (95% CI, 147-201), and 146 for women (95% CI, 120-176). Adjusted to the world population rates were 76 overall (95% CI, 59-94), 91 for men (95% CI, 73-112), and 61 for women (95% CI, 47-78). The 28-day case fatality rate for first-ever stroke was 19% (95% CI, 14-24); the majority were ischemic (84% [95% CI, 78-91]). Intracerebral hemorrhage comprised 11% (8-16), subarachnoid hemorrhage 3% (1-6), and 3% (1-6) were undetermined. Of the 258 ischemic strokes, 42% (95% CI, 36-49) were of cardioembolic pathogenesis. Atrial fibrillation accounted for 36% of all ischemic strokes, of which 85% were inadequately anticoagulated.

Conclusions—Stroke incidence in Adelaide has not increased compared with previous Australian studies, despite the aging population. Cardioembolic strokes are becoming a higher proportion of all ischemic strokes. (Stroke. 2013;44:1226-1231.)

AF and Cardioembolic Stroke
A history of previous AF or PAF was identified in 78 stroke events. New onset AF was diagnosed at presentation in 26 events, and another 11 events were diagnosed with new onset PAF with cardiac monitoring.

Of 109 cardioembolic strokes, 81 were attributed to AF and 11 to PAF by the diagnostic panel. Of all AF-related strokes, 57 (70%) patients had been diagnosed before their event. Of these, 14 were therapeutically anticoagulated, 11 patients were subtherapeutically anticoagulated, and 32 patients were unanticoagulated. All 32 had a CHADS2 score ≥2 before the event. Of those 32, 16 had no contraindication to warfarin. Of the remaining 16, 2 had a history of gastrointestinal bleeding. For the remaining 14, treating doctors cited an unacceptably high risk of falling.

Management of Atrial Fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia to affect humans, with a prevalence of ~2% in the unselected adult population. Twenty five percent of adults aged > 40 years will be diagnosed with AF in their lifetime.

- 1 in 10 of people over 80 years

Time-in-therapeutic range (TTR) is one measure of quality of anticoagulation dose management, but various methodologies exist for measuring TTR.
Different Methods

**Percent of Visits in Range** This looks at how many visits had INR results in range, and divides by the total number of visits. If the patient has had 8 visits, and 6 had readings within their therapeutic range, then the patient is considered in range 75% of the time.

**Percent of Visits in Range on Given Date**
This method takes a specific date in time, and all patients are evaluated on the last reading prior to that date to see if they were within range. The number of patients in range (on their last reading) is taken as a percentage of the total active patients on that date.

Different Methods

**Percent of Days in Range** (Rosendaal Method)
This considers the amount of time between visits to determine how long the patient might have been within their therapeutic range. If a patient has a therapeutic range of 2.0 - 3.0, and on 1\textsuperscript{st} August had an INR of 2.5, then and INR of 3.5 on 31\textsuperscript{st} August, then the number of days in range are calculated. Since there were 30 days between tests, the assumption is that the patient slowly moved from 2.5 to 3.5 over those 30 days, so around 15\textsuperscript{th} August, the patient may have been over 3.0, and therefore out of range. Therefore, using this method it is estimated that 15 days were in range, and 15 days were out of range (within the 30 day time period), which means the patient is within range 50% of the time.

The results of clinical trials often hinge on the quality of oral anticoagulation management, yet the quality of such management is frequently not mentioned or measured.

Management of Atrial Fibrillation

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

PROCEDURES

After providing written informed consent, all trial participants were randomly assigned to receive one of two doses of dabigatran, or to receive warfarin, by means of a central, interactive, automated telephone system. Dabigatran was administered, in a blinded fashion, in capsules containing either 110 mg or 150 mg of the drug, to be taken twice daily. Warfarin was administered, in an unblinded fashion, in tablets of 1, 3, or 5 mg and was adjusted locally to an international normalized ratio (INR) of 2.0 to 3.0, with the INR measured at least monthly. The time that the INR was within the therapeutic range was calculated with the use of the method of Rosendaal et al.,19 excluding INRs from the first week and after discontinuation of the study drug. These data were reported back to the participating centers with advice for optimal INR control. Concomitant use of aspirin (at a dose of <100 mg per day) or other antiplatelet agents was permitted. Quinidine use was specifically. In the warfarin group, the mean percentage of the study period during which the INR was within the therapeutic range was 64%.

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

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anticoagulant agents. In the warfarin group, we used the method of Rosendaal et al. to calculate the overall time that INR values fell within the therapeutic range. Comparative analyses of treatment efficacy were performed according to quartiles of time that INR values fell within the therapeutic range at the participating clinical sites.

rently with the assigned study drug. Among patients in the warfarin group, INR values were within the therapeutic range (2.0 to 3.0) a mean of 55% of the time (median, 58%; interquartile range, 43 to 71).

The NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Apixaban versus Warfarin in Patients with Atrial Fibrillation

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the warfarin dose. The time that patients’ INRs were within the therapeutic range was calculated by the Rosendaal method. A program was implemented to improve the quality of INR control through education and feedback at the site and country levels.

definition (P=0.001). Patients in the warfarin group had an INR in the therapeutic range (2.0 to 3.0) for a median of 66.0% of the time and a mean of 62.2% of the time, after the exclusion of INR values during the first 7 days after randomization and during study-drug interruptions.

Review of Anticoagulation Therapies in Atrial Fibrillation
**Recommendation 3 — scope of national guidelines**

In regard to anticoagulation therapies in the management of AF, the national guideline will need to consider:

- a systematic approach to risk assessment (assessment of stroke risk through algorithms such as CHADS$_2$ and CHA$_2$DS$_2$-VASc, and bleeding risk through algorithms such as HAS-BLED); therapeutic options (including addressing barriers to the optimisation of anticoagulant use); and the cost-effectiveness of therapeutic options

- nationally endorsed dosing and management algorithms for all available anticoagulants; such algorithms would need to cover situations such as initiation, frequency of monitoring for efficacy and for toxicity, adjustment of dosage when required, cessation of therapy and switching between therapies. This should also include recommendations for the calculation and use of time in therapeutic range (TTR) for warfarin

- pre-operative and peri-operative management of bleeding risk

- management of bleeding or over anticoagulation taking into account different healthcare environments and resources available to mitigate or reverse this adverse effect

- consideration of concomitant medicines and comorbid conditions, including development of a resource for alternative treatment options to medicines shown to interact with warfarin or other
TTR mostly used in the setting of clinical trials where it is used to evaluate the effectiveness of warfarin therapy, particularly when warfarin is being compared to some other strategy.

Potential to use TTR as a quality measure

There is evidence that better anticoagulation control (i.e., higher TTR) can protect patients from severe or even fatal adverse events and improve outcomes.

A study of 124,551 patients who received outpatient oral anticoagulation from 100 Veterans Administration (VA) sites of care for indications other than valvular heart disease demonstrated that risk-adjusted therapeutic international normalized ratio (INR) range (TTR) can be used as a quality indicator for oral anticoagulation care.

The authors found Risk-adjusted TTR is feasible to measure and is relatively consistent from year to year.

1.4 Self-management and self-monitoring for patients treated with a vitamin K antagonist

1.4.1 Do not routinely offer self-management or self-monitoring of INR to patients who have had DVT or PE and are having treatment with a VKA

Source: NICE clinical guidelines
Issued: June 2012
CG144
Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing
BACKGROUND

Warfarin anticoagulation reduces thromboembolic complications in patients with atrial fibrillation or mechanical heart valves, but effective management is complex, and the international normalized ratio (INR) is often outside the target range. As compared with venous plasma testing, point-of-care INR measuring devices allow greater testing frequency and patient involvement and may improve clinical outcomes.

METHODS

We randomly assigned 2922 patients who were taking warfarin because of mechanical heart valves or atrial fibrillation and who were competent in the use of point-of-care INR devices to either weekly self-testing at home or monthly high-quality testing in a clinic. The primary end point was the time to a first major event (stroke, major bleeding episode, or death).

RESULTS

The patients were followed for 2.0 to 4.75 years, for a total of 8730 patient-years of follow-up. The time to the first primary event was not significantly longer in the self-testing group than in the clinic-testing group (hazard ratio, 0.88; 95% confidence interval, 0.75 to 1.04; P=0.14). The two groups had similar rates of clinical outcomes except that the self-testing group reported more minor bleeding episodes.

Over the entire follow-up period, the self-testing group had a small but significant improvement in the percentage of time during which the INR was within the target range (absolute difference between groups, 1.8 percentage points; P<0.001). At 2 years of follow-up, the self-testing group also had a small but significant improvement in patient satisfaction with anticoagulation therapy (P=0.002) and quality of life (P<0.001).

CONCLUSIONS

As compared with monthly high-quality clinic testing, weekly self-testing did not delay the time to a first stroke, major bleeding episode, or death to the extent suggested by prior studies. These results do not support the superiority of self-testing over clinic testing in reducing the risk of stroke, major bleeding episode, and death among patients taking warfarin therapy. (Funded by the Department of Veterans Affairs Cooperative Studies Program; ClinicalTrials.gov number, NCT00032591.)