Warfarin is the single most effective treatment to prevent stroke in patients with atrial fibrillation (AF) in that it reduces the risk by about two thirds compared with placebo.1 Despite its effectiveness, however, warfarin is difficult to use and its uptake into clinical practice has been constrained.2 Warfarin has a slow onset and offset of action, it exhibits considerable variability in dose response among individuals, it is subject to multiple food and drug interactions, it has a narrow therapeutic window, and considerable risk of hemorrhage exists. The slow offset of action of warfarin can be beneficial if a patient misses a dose but complicates temporary discontinuation of warfarin for surgery. Thus, warfarin requires careful laboratory monitoring and dose adjustment to maintain the international normalized ratio (INR) in the target therapeutic range. Even with careful laboratory monitoring, major bleeding occurs in 1% to 3% of AF patients on warfarin per year. Consequently, many clinicians and patients are reluctant to use warfarin. Some patients have contraindications to anticoagulation, but others choose not to use it.3 Such patients typically use aspirin.

Educational and support programs have been shown to improve knowledge of disease and treatment, INR control, and physician management of AF.4,5 Nonetheless, there have been intensive efforts to find a replacement for warfarin. Several new drugs with the potential to overcome the limitations of warfarin have been evaluated in randomized trials but appeared to be less effective or less safe than warfarin. The experience from these trials has highlighted the methodological challenges of finding a replacement for warfarin, which include a number of difficulties in design and in interpretation of results from noninferiority trials, the widespread use of warfarin in the community, availability of warfarin-naïve patients, and low event rates on warfarin. The present article will review the results of recent phase III randomized trials that evaluated new antithrombotic agents in AF, and it will focus on the methodological challenges in the evaluation of a new antithrombotic therapy.

Underuse of Warfarin

As a consequence of pharmacokinetic and pharmacodynamic limitations, warfarin requires frequent laboratory monitoring and dose adjustment. Concern about the inconvenience of the need to undergo regular laboratory monitoring and the risk of bleeding has contributed to the underuse of warfarin in patients with AF. Immediately after the benefits of warfarin for stroke prevention in AF patients were convincingly demonstrated in 1989, its use steadily increased.2 However, recent surveys6–10 suggest that the use of warfarin has plateaued in the past few years at ≈50% to 60% of eligible patients with AF (Table 1). New anticoagulants that do not share the pharmacological limitations of warfarin have the potential to lead to an increase in the proportion of patients with AF on effective antithrombotic therapy.

Recent Phase III Trials of Novel Antithrombotic Therapies to Prevent Stroke in AF

Ximelagatran

The oral direct thrombin inhibitor Ximelagatran is a prodrug of melagatran, a small molecule that targets the active site of thrombin and blocks the enzyme’s catalytic activity. Ximelagatran produces a predictable anticoagulant response with no known drug or food interactions, which thereby reduces the need for laboratory monitoring. Two phase III noninferiority trials compared unmonitored Ximelagatran (36 mg twice daily) with dose-adjusted warfarin (target INR, 2.5; range, 2.0 to 3.0) in patients with nonvalvular AF and at least 1 additional risk factor for stroke. The Stroke Prevention Using the Oral Thrombin Inhibitor in Patients with Nonvalvular Atrial Fibrillation III (SPORTIF III)11 trial used an open-label design with blinded adjudication, whereas SPORTIF V12 was a double-blind trial that used a sham INR scheme to maintain blinding. The primary outcome measure in both trials was a combination of all strokes and systemic thromboembolism.

SPORTIF III (open-label n = 3407) showed a trend to fewer strokes in favor of Ximelagatran. The annual rates of stroke and systemic embolism were 1.6% on Ximelagatran and 2.3% on warfarin. SPORTIF V (double-blind n = 3922), on the other hand, showed results that tended to favor warfarin. The annual rates of stroke and systemic embolism were 1.6% on Ximelagatran and 1.2% on warfarin. In both trials, rates of major bleeding were somewhat lower on Ximelagatran compared with warfarin. Although some heterogeneity between
the results of the 2 SPORTIF trials was observed for the
impact on stroke, a prespecified analysis of the data pooled
from SPORTIF III and SPORTIF V was reported. The rates of
stroke and systemic embolic events were almost identical
with Ximelagatran and warfarin (1.6% per year and 1.6% per
ear; risk ratio 0.98; 95% confidence interval [CI], 0.73 to
1.30; \( P=0.98 \)). The rate of major bleeding (on treatment)
in the pooled analysis tended to be lower with Ximelagatran
(1.9% per year versus 2.5% per year; risk ratio 0.76; 95% CI,
0.56 to 1.03; \( P=0.07 \)).13

Ximelagatran failed to receive approval from the US Food
and Drug Administration. The main reason was concern
about safety; Ximelagatran was associated with raised
transaminase levels in 4% to 6% of patients and with a few
cases of fulminant hepatic failure.14 However, regulatory
authorities and other commentators14 also concluded that
noninferiority had not been established, even though both
trials satisfied their prespecified noninferiority hypotheses.
This conclusion was based on re-analysis of the noninferi-
ority margin with more conservative estimates of efficacy of
warfarin based on a somewhat different meta-analysis of
previous warfarin trials, which applied a more conservative
rule for determination of noninferiority margin and focused
on the double-blind SPORTIF 5 results in preference to the
open-label SPORTIF 3 results because of the heterogeneity
between SPORTIF III and V results.

Idraparinux
Idraparinux is a synthetic analog of the active pentasaccha-
ride sequence contained in unfractionated heparin and low
molecular weight heparin that selectively inhibits activated
Factor 10a Inhibitors
Dabigatran
Dabigatran is a novel oral direct thrombin inhibitor and a
prodrug of dabigatran etexilate. Like Ximelagatran, dabiga-
tran produces a predictable anticoagulant response with no
known drug or food interactions, which thereby reduces the
need for coagulation monitoring. The half-life of dabigatran
is \( \approx 8 \) hours after single-dose administration and up to 14 to
17 hours after multiple doses. It is usually given twice daily.17
Dabigatran is compared with warfarin (INR 2 to 3) in a very
large, ongoing, phase III, noninferiority, randomized con-
trolled trial, Randomized Evaluation of Long-Term Antico-
agulant Therapy (RELY). This trial will enroll 15 000 pa-
tients randomized to warfarin, or to 1 of 2 doses of dabigatran
(110 mg or 150 mg, twice daily). The trial will balance
enrollment between warfarin-experienced patients and those
who have received it for \( <2 \) months. The warfarin to
dabigatran comparison is unblinded and the 2 doses of
dabigatran are blinded.

Factor 10a Inhibitors
Rivaroxaban is a member of a new class of orally available,
small molecule, active-site–directed factor Xa inhibitor. It
has high bioavailability (60% to 80%) and rapid onset of
action, and it is excreted by renal (two thirds) and fecal (one
third) routes. Rivaroxaban has a half-life of 6 to 9 hours.
Apixaban is another oral factor Xa inhibitor. Rivaroxaban and
apixaban are both compared with warfarin in large phase III
trials for the prevention of stroke or systemic embolism in
patients with AF.18,19 Both trials use a single dose of

<table>
<thead>
<tr>
<th>Year Published</th>
<th>Survey</th>
<th>Population</th>
<th>Treated With Warfarin, % (Patient Status)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>ATRIA Study(^{10})</td>
<td>11 082 US patients large health maintenance organization without contraindications</td>
<td>60 (high-risk patients)</td>
</tr>
<tr>
<td>2005</td>
<td>NABOR Study(^{8})</td>
<td>945 US patients from teaching, community, and VA hospitals</td>
<td>55 (high-risk patients)</td>
</tr>
<tr>
<td>2006</td>
<td>Euro Heart Survey(^{6})</td>
<td>2706 outpatients in 35 European countries</td>
<td>64</td>
</tr>
<tr>
<td>2006</td>
<td>Hylek et al(^{7})</td>
<td>402 US patients, ( \geq 65 ) years old, not on warfarin at admission to teaching hospital</td>
<td>51 (discharged on warfarin)</td>
</tr>
<tr>
<td>2006</td>
<td>Birman-Deych et al(^{8})</td>
<td>16 007 US Medicare patients</td>
<td>49</td>
</tr>
</tbody>
</table>

ATRIA indicates Anticoagulation and Risk Factors in Atrial Fibrillation; NABOR, National Anticoagulation Benchmark and Outcomes Report.

Aspirin and Clopidogrel
The Atrial Fibrillation Clopidogrel Trial With Irbesartan for
Prevention of Vascular Events (ACTIVE)-W trial, an open-
lable randomized controlled trial (n=7606 patients), com-
pared combination aspirin (75 to 100 mg recommended) and
clopidogrel (75 mg) therapy to oral anticoagulation (INR 2 to
3) in patients with AF and at least 1 risk factor for stroke.16
Designed as a noninferiority trial, ACTIVE-W was termi-
nated early when oral anticoagulation was found to be
superior to combination antiplatelet therapy for prevention of
stroke. After a median follow-up of 1.28 years, the annual
rate of the primary outcome (a composite of stroke, systemic
thromboembolism, myocardial infarction, and vascular death)
was 3.9% in the oral anticoagulation group and 5.6% in the
combination antiplatelet therapy group (\( P=0.0003 \)).

New Agents in Phase III Trials

SanOng 34006/Idraparinux (AMADEUS) Study was an
open-label phase III trial that aimed to recruit \( >7000 \) patients
to compare subcutaneous idraparinux (given subcutaneously
once weekly without coagulation monitoring) with dose-
adjusted warfarin (target INR, 2.5; range, 2.0 to 3.0) in
patients with AF and at least 1 additional risk factor for
stroke. Designed as a noninferiority trial, the primary efficacy
outcome measure was a composite of all strokes (ischemic
and hemorrhagic) and systemic embolic events. The trial was
terminated early because of safety concerns with regard to
bleeding.

TABLE 1. Use of Oral Anticoagulant Therapy to Prevent Stroke in AF: Results of Recent Surveys

<table>
<thead>
<tr>
<th>Year Published</th>
<th>Survey</th>
<th>Population</th>
<th>Treated With Warfarin, % (Patient Status)</th>
</tr>
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<tbody>
<tr>
<td>1999</td>
<td>ATRIA Study(^{10})</td>
<td>11 082 US patients large health maintenance organization without contraindications</td>
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<td>2006</td>
<td>Birman-Deych et al(^{8})</td>
<td>16 007 US Medicare patients</td>
<td>49</td>
</tr>
</tbody>
</table>
investigational product and are double blinded. Patient enrollment in each trial is about 14 000 to 15 000 patients.

**Challenges in Evaluation of New Antithrombotic Drugs to Replace Warfarin in AF**

Several challenges exist in establishing a new antithrombotic therapy in AF. These are reviewed in Table 2 and will be discussed in detail below.

**Trial Design**

Three options exist in the design of trials for the evaluation of a new antithrombotic agent in AF. Placebo-controlled trials are desirable and ethical in low-risk patients, but low event rates and the high probability that bleeding risk will outweigh benefit make them unattractive. Alternatively, it is possible to evaluate whether a new agent is superior to aspirin because many high-risk AF patients currently receive aspirin. The final alternative is to compare a new drug to warfarin. Because it is unlikely that any new treatment will be more effective than warfarin for stroke prevention, such trials use a noninferiority design. This has been the most commonly used approach, so we will discuss it first.

**Noninferiority Trials Against Warfarin**

Ideally, one would like to be able to ensure that the new agent is totally comparable to the established agent. From the perspective of statistics, a new agent cannot be shown to be identical to standard therapy because all estimates of treatment effects have some uncertainty (CIs) around them. Therefore, the concept of noninferiority is logical and useful in trials that seek to establish a new agent by means of comparison to existing therapy. In a noninferiority trial, the goal is to demonstrate that a new agent is both superior to placebo and preserves a prespecified fraction of the benefit of standard therapy over control or placebo. Inherent in a noninferiority design is the potential for a loss of benefit. Reduced benefit of a new drug compared with the standard treatment can be justified if the loss of benefit falls within prespecified limits and if the new antithrombotic drug offers ancillary benefits such as greater ease of use, reduced need for laboratory monitoring, or possibly reduced risk of bleeding.

A key challenge in the design of any noninferiority trial is the selection of the noninferiority margin, which quantifies the minimally acceptable potential loss in efficacy of the new agent compared with standard therapy. Ideally, clinical judgment should play a key role in the decision of how much loss of efficacy is acceptable. However, given how difficult it is to formalize such judgements, a preference exists for methods that derive the margin from statistical reasoning. In AF, this approach relies on meta-analysis of prior randomized controlled AF trials to provide an estimate (and range of plausible effects through the 95% CI) of the efficacy of warfarin. Several randomized trials exist of warfarin against placebo or control in AF. Patients varied in baseline risk of stroke, and many patients were at low risk. Comparison of the new antithrombotic drug against warfarin makes it possible to estimate what the treatment effect of the new antithrombotic drug would have been if it had been tested directly against placebo. However, to show that a new agent is better than placebo is only the first step. The physician is also interested in whether the new agent is “as good as” the existing treatment. To do this, a trial sets a stricter noninferiority margin that specifies that a part of the known benefit of warfarin over placebo is to be preserved by the new therapy.

Although the statistical approach provides a measure of objectivity in determination of noninferiority margins, important uncertainties still exist. There are different ways to estimate the least likely treatment effect of warfarin, although the upper boundary of the 95% CI is usually chosen. It is still a matter of judgment to decide what fraction of the

<table>
<thead>
<tr>
<th>Issue</th>
<th>Reason</th>
<th>Consequences</th>
<th>Potential Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninferiority trial design</td>
<td>Lack of consensus on noninferiority margin</td>
<td>Overly conservative margin increases risk of rejection of effective treatments</td>
<td>Perform parallel superiority study</td>
</tr>
<tr>
<td></td>
<td>Uncertainty about historical constancy of standard treatment</td>
<td>Justifies more conservative noninferiority margin that leads to larger trial size</td>
<td>Perform on-treatment analysis; excellent execution</td>
</tr>
<tr>
<td></td>
<td>Poor execution increases likelihood of a favorable result (eg, crossover, poor INR control)</td>
<td>Potential for approval of an ineffective therapy</td>
<td>Perform parallel superiority study; conservative noninferiority margin</td>
</tr>
<tr>
<td></td>
<td>Design accepts potential loss of efficacy of the experimental treatment compared to standard</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke rates on warfarin decrease</td>
<td>More effective cointerventions</td>
<td>Reduced statistical power</td>
<td>Large sample sizes</td>
</tr>
<tr>
<td>Percentage of INR values in therapeutic range</td>
<td>No accepted benchmark</td>
<td>Poor INR control risks falsely conclude efficacy of new agent; unrealistically good control risks rejection of effective treatment</td>
<td>Establish broad consensus on benchmark</td>
</tr>
<tr>
<td>Warfarin experienced patients</td>
<td>These patients are easy to find but they are self-selected “good responders” to warfarin.</td>
<td>Increased risk of rejection of effective new treatment</td>
<td>Include appropriate mix of warfarin experienced and warfarin inexperienced patients</td>
</tr>
</tbody>
</table>
TABLE 3. Stroke Rates on Oral Anticoagulation in Large AF Trials in High-Risk Patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year Published</th>
<th>Baseline Systolic BP</th>
<th>INR in Therapeutic Range, %</th>
<th>Warfarin-Naive, %</th>
<th>Ischemic Stroke, %</th>
<th>Total Stroke, %</th>
<th>Hemorrhagic Stroke, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPAF III</td>
<td>1996</td>
<td>140</td>
<td>61</td>
<td>44</td>
<td>1.9</td>
<td>2.4</td>
<td>0.5</td>
</tr>
<tr>
<td>SPORTIF III</td>
<td>2003</td>
<td>139</td>
<td>66</td>
<td>27</td>
<td>1.9</td>
<td>2.3</td>
<td>0.4</td>
</tr>
<tr>
<td>SPORTIF V</td>
<td>2005</td>
<td>132</td>
<td>68</td>
<td>16</td>
<td>1.1</td>
<td>1.2</td>
<td>0.1</td>
</tr>
<tr>
<td>ACTIVE W</td>
<td>2006</td>
<td>133</td>
<td>64</td>
<td>23</td>
<td>1.0</td>
<td>1.4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

BP indicates blood pressure.

historically determined benefit of warfarin the agent should preserve. A conservative approach, which chooses a low estimate of the benefit standard therapy and also chooses to preserve a high fraction (≥50%) of the margin of benefit of standard therapy, leads to a very narrow noninferiority margin. This in turn increases the likelihood of false-negative results, which means that effective therapies with potential benefits will not be adopted. More liberal noninferiority margins increase the likelihood that weakly effective or even ineffective therapies will be adopted into clinical practice. An overly liberal approach is unacceptable when outcomes such as stroke and death are prevented. A conservative approach to setting the noninferiority margin is currently favored by regulatory agencies. This results in the need for very large trials in AF (typically ≈10 000 to 15 000 patients or more).

Although a Bayesian approach might be used to reduce the size of study needed, such methods have not been accepted by authorities. Use of an outcome event composite will increase event rates and can reduce sample size in superiority trials. However, in noninferiority trials in AF, little such benefit is derived from the use of a cluster of total vascular events as primary outcome because the benefit of increased events is offset by a more conservative noninferiority margin, as a result of a wider CI for total vascular events (than for stroke) in placebo-controlled trials.

Uncertainties With Noninferiority Designs

Two factors related to the design of noninferiority trials justify a conservative approach to setting the noninferiority margin: first, the potential that there will be gradual slippage of standards of approvability of new agents as a result of a series of noninferiority trials; and second, the need to assume constancy of clinical treatment over time. Noninferiority trial designs explicitly accept a potential loss of efficacy of the new agent compared with standard therapy. If the new agent becomes the new standard, this opens the possibility of further loss of efficacy when the next new agent is tested against the new standard with a noninferiority design. Eventually, some new agent could achieve noninferiority to the previous standard (which in turn was noninferior to a former standard), when in fact the new agent is no better than placebo. The solution to this concern, which is to have very conservative noninferiority margins, may be so onerous an obstacle to evaluation of the first new agent in AF that the sorts of trials needed may simply be impractical.

A more fundamental concern is the assumption of constancy of clinical practice. The critical margin of noninferiority in trials performed today is set on the basis of results of trials done in the past. One therefore implicitly assumes that the efficacy of standard therapy has remained generally constant into the current era. This constancy assumption cannot be proven because a placebo arm does not exist in the noninferiority trial. The constancy assumption may not hold because clinical practice in fact does evolve over time. A conservative approach to the setting of noninferiority margins has been recommended as a solution and is especially justifiable when concern exists that the standard treatment is less effective today than in the past. Under such circumstances, a new drug might be able to demonstrate noninferiority to a now less effective standard therapy even though the new drug is not better than placebo.

The management of patients with AF has changed since randomized controlled trials of warfarin were first performed >15 years ago and now include better control of blood pressure and increased use of drugs such as statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. Evidence also exists, based on lower stroke rates in recent trials, that warfarin may be used more effectively today than in the previous generation of trials (see first paragraph of Improved INR Control and the Challenge for Modern Trials and Table 3). Such a change might justify a more liberal noninferiority margin, as the standard therapy may have become harder to match. Most researchers and regulators feel uncomfortable with this approach, but the margins chosen for noninferiority trials should be based on all available evidence. In summary, important regulatory concerns about noninferiority trial design and its long-term implications for the drug approval process have led to a conservative approach to setting the noninferiority margin. This sets a high standard for new agents to achieve, compared with the original standards where trials have evaluated the superiority of agents versus placebo therapy. Table 2 summarizes key features of noninferiority trial design.

Superiority Trials Against Aspirin

A superiority trial of a new agent against aspirin is ethical and feasible in high-risk patients with AF. As shown in Table 1, many patients exist who cannot or will not take warfarin. Some of these have increased risk of bleeding and are not suitable for a trial of antithrombotic therapy. However, others have compliance issues specifically related to vitamin K antagonists, and these patients may be able to safely use an antithrombotic agent that does not require monitoring. Recent guideline changes indicate that AF patients with a single
risk factor may receive either warfarin or aspirin. These patients are at lower risk of events, and this would mean that, if they were the only patients enrolled, the study size could be very large. This is offset in part by the fact that superiority trials designed to detect fairly large treatment effects (35% to 45% relative risk reduction) require far fewer patients and events than noninferiority trials in AF.

An important synergy exists in the performance of a superiority trial against aspirin in support of a noninferiority trial against warfarin, with the same therapeutic agent, in the 2 populations of AF patients at high risk for stroke. Trials that demonstrate superiority of a new agent over an existing agent or placebo provide the most direct way to establish the efficacy of the new agent. Unlike noninferiority trials, superiority trials do not require interpretation of a meta-analysis of previous trials, do not require agreement on a noninferiority margin, and do not make assumptions about historical constancy of treatment effects. Also unlike noninferiority trials, superiority trials do not raise concerns about the balance of the potential loss of efficacy and also face less serious problems when noncompliance with the study drug is prominent. Although most investigators would be hesitant to accept a superiority trial against aspirin as pivotal for development of a new antithrombotic agent, few would disagree that clear evidence of substantial efficacy of a new agent against aspirin would provide support to an application for approval based on a noninferiority trial against warfarin.

Evaluation of the feasibility of a superiority trial against aspirin in AF patients at moderate to high risk is a goal of the ongoing Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE A) trial, which compares clopidogrel plus aspirin to aspirin therapy alone. It has completed enrollment of 7645 high-risk AF patients in >30 countries and 500 centers worldwide and will report results in 2008.26

### Declining Event Rates

Rates of strokes in AF trials appear to be declining over time (Table 3). The primary prevention randomized controlled trials before 1995 did not select high-risk AF patients.27 In the pooled analysis of these trials, 35% of patients were <65 years of age and had no risk factors for stroke. With the publication in 1996 of Stroke Prevention in Atrial Fibrillation (SPAF) 3, AF trials have only included patients with risk factors for stroke.28 SPAF 3 reported an ischemic stroke risk on warfarin of 1.9% per year. Trials published recently generally report much lower rates of ischemic stroke on warfarin or vitamin K antagonists: 1.9% per year in SPORTIF 3 (2003), 1.1% per year in SPORTIF 5 (2005), and 1.0% per year in ACTIVE W (2006) (Table 3). The lower risk of ischemic stroke on warfarin, despite selection of high-risk patients in recent trials, may be related to more effective concomitant therapies, more aggressive control of systemic hypertension, and improved control of oral anticoagulant therapy. The last decade has seen an increased use of statin therapy and more aggressive treatment of blood pressure with increased use of angiotensin-converting enzyme inhibitors and angiotensin receptor blocking drugs. The mean systolic blood pressure at baseline in the pooled analysis of the controlled trials of warfarin in AF27 was 141 mm Hg and in SPAF 3 was 140 mm Hg.28 The corresponding baseline mean systolic blood pressures in SPORTIF 3, SPORTIF 5, and ACTIVE W were 139 mm Hg, 132 mm Hg, and 133 mm Hg, respectively. Very low event rates on warfarin create a challenge for study design. If the total rate of ischemic hemorrhagic stroke and systemic embolism is only 1.5% per year, 30 000 patient years of follow-up are needed to have the 450 events required in a typical noninferiority trial in AF. By contrast, a total of only 108 ischemic strokes (from 3706 patients) are reported in the pooled data from the first 5 trials of warfarin against placebo or control in AF.1

### Improved INR Control and the Challenge for Modern Trials

INR control of warfarin therapy has improved since the first trials with warfarin were performed. At the time of the first 5 placebo-controlled trials, use of the INR to control warfarin was just being introduced clinically in North America, and 3 of the 5 studies controlled warfarin by means of the prothrombin time ratio.29–31 This method is inferior to the use of the INR because it does not correct for the variable characteristics of different thromboplastin reagents and is likely to lead to less optimal INR control. INR was used to monitor anticoagulation in 2 of the original placebo-controlled trials (Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation [AFASAK] study32 and Canadian Atrial Fibrillation Anticoagulation [CAFA] study33), in which the percentages of INR values in the target range were 42% and 44%, respectively. In the recent SPORTIF 3, SPORTIF 5, and ACTIVE W trials, the time in therapeutic range of the INR was 66%, 68%, and 64%, respectively.

The relationship between INR control and both embolic and hemorrhagic outcomes is well established, and improved INR control will result in lower event rates on warfarin.34,35 This makes modern warfarin therapy a formidable comparator therapy and creates a dilemma for noninferiority trial design and conduct. In a noninferiority trial, should one target the rates of INR control observed in the original placebo-controlled trials, or a level typically achieved in clinical practice, or the best possible level of INR control? Insistence on the latter may demand a level of rigor that is artificial and inconsistent with the constancy principle of noninferiority trials. If one uses the former approach, the investigators may run the risk of not using best possible therapies.

### Potential for Different Treatment Effects in Warfarin-Naïve and Warfarin-Experienced Patients

Another challenge for the design of antithrombotic trials in AF is the widespread use of warfarin therapy in specialists’ practices in Western countries. Because patients are most easily recruited into clinical trials from such practices (especially from anticoagulant clinics), a tendency exists to enroll patients already on successful warfarin treatment for years. Such patients are thus likely to be self-selected “responders” to warfarin because patients with a tendency to hemorrhage on warfarin, or in whom INR control is difficult, will self-identify during prestudy exposure to warfarin. In recent
Event rates in patients on and not on oral anticoagulants at entry to the ACTIVE W trial. Reproduced from the ACTIVE Writing Group, with permission from Elsevier. Copyright 2006.

Evaluation of new antithrombotic agents for AF is challenging. We have discussed the commonly used trial design of noninferiority and alternatives to this approach. We have discussed the assumptions inherent to noninferiority trial design and some of the complexities of trial conduct, both of which complicate interpretation of results. Noninferiority trial design is still evolving, and regulatory agencies mandate conservative noninferiority margins. This, together with declining stroke rates in AF patients on warfarin, leads to a requirement for very large patient enrollments (≥15 000) and a real risk of false-negative results. The enrollment challenge is compounded because the easiest approaches (eg, anticoagulation clinics) to identify high-risk patients for these trials leads to the enrollment of warfarin-experienced individuals. These patients have had a chance to discover whether or not they respond well to warfarin but not to the new agent. The efficacy of warfarin may have improved over time with improved INR control and advances in concomitant therapy for hypertension. A superiority trial design, which compares a new agent against aspirin, could be performed as a complement to a noninferiority trial. Three new antithrombotic strategies that use noninferiority designs have been recently evaluated in AF without success. The experience from these trials has highlighted some of the challenges and should enable the design of better programs for the evaluation of new antithrombotic drugs in AF. Promising new agents will be tested in the next few years.

Conclusion

Evaluation of new antithrombotic agents for AF is challenging. We have discussed the commonly used trial design of noninferiority and alternatives to this approach. We have discussed the assumptions inherent to noninferiority trial design and some of the complexities of trial conduct, both of which complicate interpretation of results. Noninferiority trial design is still evolving, and regulatory agencies mandate conservative noninferiority margins. This, together with declining stroke rates in AF patients on warfarin, leads to a requirement for very large patient enrollments (≥15 000) and a real risk of false-negative results. The enrollment challenge is compounded because the easiest approaches (eg, anticoagulation clinics) to identify high-risk patients for these trials leads to the enrollment of warfarin-experienced individuals. These patients have had a chance to discover whether or not they respond well to warfarin but not to the new agent. The efficacy of warfarin may have improved over time with improved INR control and advances in concomitant therapy for hypertension. A superiority trial design, which compares a new agent against aspirin, could be performed as a complement to a noninferiority trial. Three new antithrombotic strategies that use noninferiority designs have been recently evaluated in AF without success. The experience from these trials has highlighted some of the challenges and should enable the design of better programs for the evaluation of new antithrombotic drugs in AF. Promising new agents will be tested in the next few years.
and hopefully some of these will be demonstrated to be effective, years, and safer, of course, will be easier to use than warfarin.

Disclosures

Dr Connolly and Yusuf have received research grant support from Sanofi Aventis, Bristol-Myers Squibb, and Boehringer Ingelheim for management of the ACTIVE and RELY trials, and both have given lectures and performed other consulting tasks for these companies. Dr Yusuf has served as a consultant/advisory board member for GlaxoSmithKline. The other authors report no conflicts.

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