New-onset atrial fibrillation and warfarin initiation: High risk periods and implications for new antithrombotic drugs

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Summary
Atrial fibrillation is a common condition that increases the risk of stroke in many patients. Although warfarin has been shown to reduce the risk of stroke, many patients who might benefit from anticoagulation do not receive this therapy. Fear of bleeding is the most often cited reason. Several new anticoagulant medications are being studied to determine their efficacy and safety relative to warfarin. Unlike earlier trials that established the superiority of warfarin over placebo, recent trials in atrial fibrillation have enrolled a disproportionate number of patients already taking warfarin. This review suggests that the risk of both haemorrhage and stroke are highest when atrial fibrillation is newly diagnosed and during the initiation of anticoagulant medication. Randomised controlled trials designed to evaluate the safety and efficacy of new antithrombotic agents should include substantial numbers of patients without prior exposure to anticoagulation since these individuals are at the highest risk for bleeding and thromboembolism.

Keywords
Clinical trials, oral anticoagulants, thrombosis, stroke prevention, heart failure

Introduction
Atrial fibrillation (AF) is a common dysrhythmia; its prevalence is increasing as the population ages (1). Recent projections indicate that by the year 2020, 7.5 million people in the United States will live with AF (2). Because AF results in disorganised electromechanical activity that promotes intra-atrial thrombus formation, the risk of embolic stroke is significant for many patients. The attributable risk of stroke from AF increases significantly with age, from 1.5% for individuals aged 50 to 59 years to 23.5% for individuals aged 80 to 89 years (3). Cardioembolic strokes are associated with substantial morbidity and mortality (4–8).

Between 1989 and 1993, the efficacy of warfarin for stroke prevention in AF was demonstrated decisively by five randomised controlled trials (9–13). Compared to placebo, warfarin use was associated with a 68% relative risk reduction of stroke (14). Despite this dramatic benefit, numerous studies have documented that warfarin is prescribed to only about 50% of at-risk patients with AF (15–18). Older age and perceived bleeding risk are often cited as reasons for not prescribing warfarin. In addition, the narrow therapeutic index of warfarin (combined with its variable dose-response) mandates frequent monitoring which, for many patients, precludes its use (19, 20). Newer antithrombotic agents that match the efficacy of warfarin while also offering a wider therapeutic index would likely increase the use of stroke prevention medications among patients with AF.

The first such new agent to be evaluated was ximelagatran, an oral direct thrombin inhibitor. This drug was studied in two clinical trials enrolling an unprecedented 7,329 patients with AF (SPORTIF-Stroke Prevention using an ORal Thrombin Inhibitor in atrial fibrillation). Based on the previous, placebo-controlled trials conducted in the late 1980s, a primary event (stroke or systemic embolism) rate of 3.1% per year was projected for the patients assigned to receive warfarin (21, 22). Although these studies included elderly populations with a high prevalence of stroke risk factors (Table 1), the annual rate of all strokes (ischaemic and haemorrhagic) among patients randomised to warfarin was 2.3% (SPORTIF III) and 1.2% (SPORTIF V), both lower than the pre-trial estimates. This unexpectedly low rate of thrombotic events among AF patients randomised to warfarin was also reported in a large trial comparing warfarin to dual antiplatelet therapy. In the Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W) trial, among the 3,371 patients assigned to oral anticoagulation therapy, the rate of stroke (ischaemic or haemorrhagic) plus systemic embolus was 1.5%, also lower than initial projections (23). Similarly, the Birmingham Atrial Fibrillation Treatment of the Aged study (BAFTA) reported low annual stroke rates in both treatment arms (1.8% for warfarin and 3.8% for aspirin (25).
Table 1: Clinical characteristics of AF populations randomised to warfarin.

<table>
<thead>
<tr>
<th></th>
<th>AFI (14)</th>
<th>SPORTIF III (21)</th>
<th>SPORTIF V (22)</th>
<th>ACTIVE W (23)</th>
<th>RE-LY (24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean</td>
<td>69</td>
<td>70</td>
<td>72</td>
<td>70</td>
<td>72</td>
</tr>
<tr>
<td>Gender, male, %</td>
<td>75</td>
<td>70</td>
<td>69</td>
<td>66</td>
<td>63</td>
</tr>
<tr>
<td>Heart failure, %</td>
<td>20</td>
<td>34</td>
<td>40</td>
<td>31</td>
<td>32</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>45</td>
<td>72</td>
<td>81</td>
<td>82</td>
<td>79</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>13</td>
<td>22</td>
<td>25</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>Prior stroke/TIA, %</td>
<td>6</td>
<td>24</td>
<td>18</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>VKA at entry*, %</td>
<td>10</td>
<td>73</td>
<td>85</td>
<td>78</td>
<td>49</td>
</tr>
</tbody>
</table>

AFI, Atrial Fibrillation Investigators; SPORTIF, Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation; ACTIVE, Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; TIA, transient ischaemic attack; VKA, vitamin K antagonist. Defined differently across trials.

Although it is possible that the rate of stroke in AF has decreased since the early trials, an alternative hypothesis is that recent trials have enrolled patients who were at lower risk of stroke, despite the similar (or increased) prevalence of stroke risk factors shown in Table 1. Unlike earlier trials designed to establish the superiority of warfarin versus placebo, more recent trials of novel antithrombotic strategies have been designed to establish non-inferiority to warfarin. Thus, the majority of participants in recent trials were taking a vitamin K antagonist (VKA) at baseline. In SPORTIF III and V, 73% and 85%, respectively, of patients randomised to warfarin had been taking a VKA at study entry. The onset of AF was documented to be greater than one year prior to study entry for ≥80% of study participants. Similarly, in the ACTIVE W trial, 77% of participants were taking warfarin at the time of randomisation (warfarin-experienced patients) and duration of AF was six months or greater for 80% of patients and greater than two years for 59% (23). The high proportion of participants who entered these trials already taking warfarin (i.e. “warfarin-experienced”) has been an under-appreciated significant difference from earlier AF trials in which greater than 90% of patients were receiving a VKA for the first time (i.e. “warfarin-naive”). A post-hoc analysis of the SPORTIF trial data suggested that the higher proportion of warfarin-naïve participants enrolled in SPORTIF III coupled with greater variability in the INR (International Normalised Ratio) contributed to the higher stroke rate in SPORTIF III versus SPORTIF V (26).

The importance of studying “new users” of a drug has been previously highlighted by Feinstein and Ray (27, 28). The efficacy and safety of new antithrombotic drugs for stroke prevention in AF can be best evaluated among patients who are new to anticoagulant therapy. Consideration of five key elements will demonstrate the chronology bias and survivor bias that impact trials that are dominated by warfarin-experienced patients: 1) bleeding risk during the early phase of anticoagulant therapy, 2) temporal relationship of stroke risk and incident AF, 3) differential early cessation of warfarin therapy among higher risk patients secondary to problems with adherence and tolerability, 4) improved efficacy of warfarin over time resulting from improved control of the INR and decreased INR variability, and 5) potential secondary benefits associated with monthly interface with health care providers (e.g. improved blood pressure control, improved rate control, improved adherence to warfarin and other stroke-modifying therapies), i.e. adherence bias.

I. Major haemorrhage: warfarin-naïve vs. warfarin-experienced

A number of studies have demonstrated that the risk of bleeding on anticoagulant therapy is highest during the period immediately after warfarin is initiated. Landefeld et al. performed a review of medical records from 565 patients prescribed warfarin (for conditions such as AF, venous thromboembolism [VTE] and heart valve replacement) upon hospital discharge. All patients in this cohort were warfarin-naive. The proportion of patients who experienced major bleeding during the first 30 days of outpatient treatment was 3%, 10-fold higher than the calculated monthly risk (0.3%) observed during the subsequent 11 months of follow-up (29). Similarly, in an analysis of data from a randomised controlled trial involving 1,021 patients being started on anticoagulation for VTE, Douketis et al. describe a significant early risk of major haemorrhagic events. Of the 28 major bleeds that occurred during the three months of warfarin treatment in this trial, 21 had occurred within three weeks and 13 had occurred within the first seven days of anticoagulant therapy (30). A meta-analysis of randomised controlled trials or prospective cohort studies of patients being treated for VTE also described a clustering of major bleeding events at the start of anticoagulant therapy: the rate of intracranial haemorrhage (expressed per 100 patient-years) was 5.92 during the first three months of anticoagulant therapy and 0.65 thereafter (31).

A retrospective, multi-center study of 928 consecutive warfarin-treated patients from five anticoagulation clinics yielded similar findings. In order to minimise survivor bias, this analysis included the records not only of patients actively receiving warfarin, but also of patients whose warfarin had been discontinued in the
previous 18–24 months. During a mean duration of follow-up of 1.9 years, being in the early phase of treatment was identified as an independent risk factor for major bleeding. In the first three months of treatment, “serious” bleeding occurred at a rate of 21 episodes per 100 patient-years. The authors found that, compared to the rest of the first year, the second year, and anytime thereafter, the relative risk for serious bleeding during the first three months of treatment was 1.9 (95% confidence interval [CI] 1.3–3.0), 3.0 (95% CI 1.8–4.8), and 5.9 (95% CI 3.8–9.3), respectively (32). When comparing the rate of major haemorrhage during the first 90 days of treatment to the rate of the same outcome after one year of warfarin exposure, a Danish study of warfarin-naïve patients reported a similar increase: incidence rate ratio, 1.9 (95% CI 0.8–4.1) (33). Table 2 summarises the evidence that the risk of warfarin-associated bleeding is highest during the initial weeks of treatment. In an evaluation of all 21,785 patients enrolled in an acute coronary syndrome registry, 2,921 patients were found to have AF (1,700 pre-existing, 1,221 newly diagnosed). Compared to patients in this registry without AF, the patients with AF had increased morbidity and mortality. However, only new-onset AF was independently associated with an increased risk of several adverse events, including in-hospital major bleeding (34). Similar results have been demonstrated in a pooled analysis of over 120,000 trial participants with acute coronary syndromes as well as in a group of almost 6,000 patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention (35, 36). Another large study, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, has reported similar findings: when compared to patients who entered the trial with a prior history of AF, major haemorrhage was reported to be more common among patients with new-onset AF (37). As noted by Ray, patients initiating therapy are often sicker than prevalent users (28).

This association of major bleeding with newly diagnosed (i.e. not pre-existing) AF provides further evidence that a group of patients being exposed to anticoagulation for the first time will have

### Table 2: Summary of evidence that the risk of bleeding is highest during the initial days of anticoagulant treatment.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design + patient population</th>
<th>Length of follow-up</th>
<th>Evidence for “front-loading” of bleeding risk</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Landefeld, 1989 (29)</td>
<td>Retrospective study of patients starting warfarin for a variety of indications</td>
<td>48 months</td>
<td>The monthly risk of major bleeding decreased over time from 3% during the first month to 0.3% per month after the first year of therapy.</td>
<td>All patients identified at the time of hospital discharge</td>
</tr>
<tr>
<td>Douketis, 2000 (30)</td>
<td>Analysis of RCT database with 1,021 VTE patients new to warfarin</td>
<td>3 months</td>
<td>28 major bleeds occurred during the initial 3 months of anticoagulation – 21 (75%) of these had occurred with 3 weeks and 13 (46%) had occurred within 7 days of starting anticoagulation</td>
<td>All patients received LMWH &quot;overlap&quot; therapy for the first days of treatment; no AF patients included</td>
</tr>
<tr>
<td>Linkins, 2003 (31)</td>
<td>Meta-analysis of 29 RCTs and 4 prospective cohort studies of VTE patients receiving oral anticoagulant therapy for at least 3 months</td>
<td>Variable, but ≥3 months in all cases</td>
<td>Intracranial bleeding during first 3 months of treatment occurred in 1.48% (95% CI 1.40% to 1.56%) of patients. After the first 3 months, the rate of intracranial bleeding was 0.65 (95% CI 0.63 to 0.68) per 100 patient-years.</td>
<td>Definitions of major bleeding differed across studies</td>
</tr>
<tr>
<td>Fihn, 1993 (32)</td>
<td>Retrospective study of 5 anticoagulation clinics; 928 patients receiving warfarin for a variety of indications</td>
<td>Median = 1.9 years</td>
<td>Compared to the rest of the first year, the second year, and anytime thereafter, the relative risk for serious bleeding during the first 3 months of treatment was 1.9 (95% CI 1.3–3.0), 3.0 (95% CI 1.8–4.8), and 5.9 (95% CI 3.8–9.3) respectively.</td>
<td>Retrospective study, some of the participating centers were not using INR (rather PT ratios) during part of the study</td>
</tr>
<tr>
<td>Steffensen, 1997 (33)</td>
<td>Retrospective, single-center cohort study of 682 warfarin-naïve patients being anticoagulated for a variety of reasons</td>
<td>756 treatment-years</td>
<td>The risk of a first major haemorrhagic episode was highest during the first 90 days of treatment; compared with treatment duration above one year, the incidence rate ratio was 1.9. Although this incidence rate ratio did not reach statistical significance, the numeric difference is consistent with other studies cited</td>
<td></td>
</tr>
<tr>
<td>Hylek, 2007 (43)</td>
<td>Prospective, single-center cohort study of 472 warfarin-naïve patients being anticoagulated for AF</td>
<td>12 months</td>
<td>15 of 26 major hemorrhages occurred with 90 days, 11 of 26 within 30 days and 7 within the first 2 weeks of warfarin therapy</td>
<td>32% of patients were ≥80 years of age, 33% were identified at hospital discharge, 40% were also taking aspirin</td>
</tr>
</tbody>
</table>

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a higher risk of haemorrhage than a group of prevalent users of oral anticoagulation. This may be related to patient-specific, period-specific, or drug-specific factors. Patient-specific factors include the unmasking of subclinical underlying pathologic lesions, labile INR measurements, and concomitant prevalent medications (e.g., anti-platelet therapy) that increase bleeding risk. Period-specific factors confer a transient increase in bleeding risk that would be expected to resolve within a short period of time. For example, the immediate post-hospitalisation period might be characterised by increased use of heparin transition therapy or dietary fluctuation; recently discharged populations will also have a higher prevalence of acute illness (e.g., gastrointestinal mucosal injury, stress-induced gastritis) associated with haemorrhage. Drug-specific factors include half-life, variability in dose-response, tendency toward erratic anticoagulation control with warfarin initiation, and individual rate of INR decay following an episode of excessive anticoagulation. For all of these reasons, it is important that the haemorrhagic risk profile of new anticoagulant drugs with different pharmacokinetic properties be assessed during the period of highest risk, i.e. the 90-day period following therapy initiation.

II. Temporal risk of stroke

Similar to major haemorrhage, the incidence of stroke is also time-dependent. The highest risk of stroke exists at the time of initial presentation with AF. In a registry of 5,477 patients with acute myocardial infarction and left ventricular dysfunction, 1,000 patients had concomitant AF; 655 of these individuals had AF at baseline (pre-existing) and 345 developed AF during the follow-up (median 3.0 years). The adjusted hazard ratio (HR) for 30-day risk of stroke among patients with new-onset AF was 14.6 (95% CI 5.87 – 36.3). In contrast, the adjusted HR for stroke during the whole trial among patients with new-onset AF was 2.29 (95% CI 1.43 – 3.68) (38).

<table>
<thead>
<tr>
<th>Event type</th>
<th>Time interval (days)</th>
<th>Person-years at risk</th>
<th>No. of events</th>
<th>No. of censors</th>
<th>Hazard per year of risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleed</td>
<td>0 – 30</td>
<td>20.6</td>
<td>4</td>
<td>15</td>
<td>0.187</td>
</tr>
<tr>
<td></td>
<td>31 – 90</td>
<td>35.4</td>
<td>4</td>
<td>57</td>
<td>0.116</td>
</tr>
<tr>
<td></td>
<td>91 – 365</td>
<td>68.8</td>
<td>3</td>
<td>113</td>
<td>0.033</td>
</tr>
<tr>
<td></td>
<td>1 – 4.2 years</td>
<td>87.3</td>
<td>7</td>
<td>58</td>
<td>0.068</td>
</tr>
<tr>
<td>Any embolism</td>
<td>0 – 30</td>
<td>20.8</td>
<td>7</td>
<td>12</td>
<td>0.328</td>
</tr>
<tr>
<td></td>
<td>31 – 90</td>
<td>35.3</td>
<td>5</td>
<td>62</td>
<td>0.146</td>
</tr>
<tr>
<td></td>
<td>91 – 365</td>
<td>66.7</td>
<td>3</td>
<td>110</td>
<td>0.034</td>
</tr>
<tr>
<td></td>
<td>1 – 4.2 years</td>
<td>84.8</td>
<td>3</td>
<td>59</td>
<td>0.030</td>
</tr>
</tbody>
</table>

Table 3: Risk of haemorrhage or thromboembolic stratified by duration of anticoagulation with warfarin. These data come from a population-based retrospective cohort study that included all residents of Rochester, Minnesota for whom a course of warfarin therapy intended to last for more than four weeks was initiated between September 1, 1987 and December 31, 1989 (39).
lant therapy; many such patients will have their warfarin discontinued. Thus, the patients remaining on warfarin will also be at lower risk for haemorrhage. The potential for survivor bias that is introduced by enrolling predominantly prevalent users of warfarin is illustrated by two examples. First, in a cohort study of 472 patients with AF newly starting warfarin, both haemorrhagic events and unplanned discontinuations of therapy occurred more frequently among patients at highest risk of stroke. The risk of stopping warfarin therapy peaked early among patients aged 80 years and older and was similar to that of younger patients at six months (43) (Fig. 1). Another study of Medicare beneficiaries tracked adherence to warfarin and INR monitoring post-hospital discharge. The authors found that a subgroup of patients, black and Hispanic individuals, at high baseline risk for stroke were more often lost to follow-up within the first 90 days than their white counterparts (whose baseline stroke risk was lower) (19). Not surprisingly, the black and Hispanic patients in this cohort ultimately suffered higher annual stroke rates (11% and 12% vs. 5% among white patients). Taken together, these studies further emphasize the lower risk profile of patients who manage to remain on warfarin for extended periods of time.

IV. The anticoagulant effect of VKAs stabilises over time

Stability of anticoagulant effect is often not achieved for several months after initiating a VKA. Fluctuations are influenced by diet, drug interactions, genetic variation, and adherence. In a study of 2,223 patients with non-valvular AF, 52% of the INR values were outside the target range (INR 2.0 to 3.0) in the first month, whereas only 30% of INR measurements were not therapeutic after two years of monitoring time (44). Similarly, among 600 adults with AF randomly sampled from three health plans, patients newly started on warfarin at the time of referral to a dedicated anticoagulation clinic tended to have poorer control than patients already taking warfarin (adjusted odds ratio [OR] 0.59; 95% CI 0.35 to 1.08) (45). A comparable association of better anticoagulant control with increased time on warfarin was seen in a study of 254 subjects taking one of three fixed doses of ximelagatran or dose-adjusted warfarin. At study entry, 61% were warfarin-experienced. Among the patients assigned to warfarin, attainment of optimal INR increased from 34% at the start of therapy to 57% at 12 weeks (46).

Enrolment of warfarin-experienced patients in randomized trials confers an advantage to the group assigned to receive warfarin. Because these patients have taken warfarin for an extended period of time, they have become familiar with their own triggers for poor INR control. This training effect results from monthly INR measurements recommended for all warfarin-treated patients. In the ACTIVE W trial of warfarin versus dual antiplatelet therapy, warfarin-naïve patients had less time in the 2.0 to 3.0 range when compared to those who entered the trial on warfarin (warfarin experienced), 60.4% versus 64.8% (p<0.001). Warfarin-naïve patients also spent more time with a sub-therapeutic INR, 24.6% versus 19.2% (p<0.001). At three months of follow-up, time in the therapeutic range for the warfarin-naïve group was 57.2% versus 62.4% for the warfarin-experienced group. Not surprisingly, the rates of both vascular events and major haemorrhage were higher in the warfarin-naïve versus warfarin-experienced

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group. Patients who entered the trial already on warfarin were also less likely to discontinue the drug, 8.7% versus 15.3% at one year (23). White et al. studied the relationship between INR control and outcomes among 3,587 patients randomised to warfarin in the trials comparing ximelagatran to warfarin. The poor control group, defined as having less than 60% of time with a therapeutic INR, experienced higher rates of major bleeding, thromboembolic events, and annual mortality. Among the reference "good" control group (defined as spending greater than 75% of time with an INR between 2.0 and 3.0), 85% of the individuals entered the study taking warfarin. In contrast, the proportion of warfarin-experienced patients in the corresponding poor (70.8%) and moderate (81.9%) control groups was lower (p<0.001) (47). Again, these findings suggest that patients who have taken warfarin for at least several months will spend more time with a therapeutic INR than patients who are new to warfarin.

V. Secondary benefits of frequent medical contact

In addition to the adherence bias introduced by warfarin-experienced patients, long-term use of a medication may be a marker of a more adherent patient population overall. Adherence to antihypertensive medication, lifestyle measures, lipid-lowering agents and diabetes treatment regimens may all collectively decrease an individual’s risk of stroke and other thrombotic events over time. The monthly interface with health care providers that occurs with each INR measurement would fortify efforts to control blood pressure, facilitate laboratory monitoring (e.g. measurement of glycated haemoglobin or lipids), minimise patient confusion over treatment plans, and reinforce treatment compliance.

Practical challenges to enrolling warfarin-naïve patients

Enrolling a high proportion of warfarin-naïve patients to participate in a clinical trial is challenging for several reasons. First, patients who are newly starting anticoagulant therapy will be far fewer in number compared to the prevalent user pool. This relative paucity of potential candidates is important because, unlike early placebo-controlled trials that enrolled approximately 250 patients in each arm, trials of non-inferiority require thousands of patients. Warfarin-naïve patients are also more likely to have acute medical conditions that might reduce the likelihood they would be approached about participating in a clinical study. Finally, for patients already taking warfarin, there is no “time limit” during which they need to be randomised. In contrast, the enrolment of patients with newly diagnosed AF is complicated by the fact that they can be considered warfarin-naïve only for a finite period. Given the time-intensive efforts necessary for patient identification, screening, consent, and randomisation, real barriers exist to enrolment of a true inception cohort of patients within a trial setting.

Conclusions

Enrolment of predominantly warfarin-experienced patients in clinical trials results in under-ascertainment of early events associated with initiation of anticoagulant therapy and newly diagnosed AF. The “warfarin surviving” patients also may introduce an adherence bias because of improved INR and blood pressure control over time. Before definitive conclusions about the relative safety and efficacy of novel anticoagulant drugs can be drawn, it is important that each of these agents be studied in warfarin-naïve patients because these patients are at the highest risk for both stroke and major haemorrhage.

Conflicts of interest

Dr. Garcia has served in an advisory capacity for Boehringer Ingelheim, Bristol-Myers Squibb, and Ortho McNeill Jansen. Dr. Lopes has received research funding from Bristol-Myers Squibb. Dr. Hylek has served in an advisory capacity for Astellas, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Genentech, Merck, Medtronic, Pfizer, and Sanofi-Aventis and received research funding from Bayer Healthcare and Bristol-Myers Squibb.

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