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Anticoagulation in atrial fibrillation: selected controversies including optimal anticoagulation intensity, treatment of intracerebral hemorrhage

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Abstract Clinical trials during the past 20 years have revolutionized the antithrombotic management of atrial fibrillation. Based on consideration of 30 randomized trials involving 29,017 participants, adjusted-dose warfarin remains the most efficacious prophylaxis against stroke for atrial fibrillation patients at moderate-to-high risk (compared with antiplatelet agents, warfarin reduces stroke by about 40%). The optimal INR for prevention of stroke for most atrial fibrillation patients is probably 2.0–2.5; INRs of 1.6–1.9 provide substantial protection, 80–90% of that afforded by higher intensities. Warfarin-associated intracerebral hemorrhage is an increasing problem as more elderly patients with atrial fibrillation are anticoagulated. Modest reductions in blood pressure results in large decreases in this most dreaded complication of warfarin; anticoagulation of elderly atrial fibrillation patients should be accompanied by a firm commitment to control hypertension. Warfarin-associated intracerebral hemorrhage has a 50% early mortality. A wide range of acute treatments to urgently reverse anticoagulation have been recommended by experts, but prevention is a far better option than treatment of this devastating problem.

Keywords Anticoagulation · Warfarin · Atrial fibrillation · Intracerebral hemorrhage · Anticoagulation intensity

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Introduction

As recently as the late 1980s, atrial fibrillation was a neglected etiology of stroke. During the last two decades, there has been an explosion of high-quality clinical data that has revolutionized management of this common cardiac dysrhythmia. Here, selected controversial issues are discussed relevant to antithrombotic management, including the optimal INR for stroke prevention in atrial fibrillation patients and the management of warfarin-associated intracerebral hemorrhage.

Antithrombotic therapies for stroke prevention

Treatment with adjusted-dose warfarin provides strong protection against stroke in patients with non-valvular atrial fibrillation, virtually eliminating the excess ischemic strokes associated with atrial fibrillation if the intensity of anticoagulation is adequate. Antiplatelet agents offer more modest protection (about a 20% stroke reduction) [1] and appear to have their major effect on the non-disabling non-cardioembolic strokes from which elderly, often hypertensive atrial fibrillation patients are not spared. To date, 30 randomized clinical trials involving 29,017 participants have tested various antithrombotic agents comparing with

placebo/control or with one another [1, 2]. Compared with antiplatelet therapies based on a metanalysis of 12 randomized trials involving 12,721 participants (by intention-to-treat analysis), adjusted-dose warfarin reduced all stroke (combining ischemic stroke and intracranial hemorrhage) by 39% (95%CI 27,49) (Table 1) [1, 2].

Two recently published randomized trials warrant comment. The large trial Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events—Warfarin (ACTIVE-W, 6706 participants) comparing the combination of clopidogrel plus aspirin (i.e. combination antiplatelet therapy) with adjusted-dose warfarin showed a large relative risk reduction by warfarin (40%) similar to that expected from comparison with aspirin alone (39%) [1, 3]—that is, addition of clopidogrel to aspirin did not appear to protect against stroke more than that expected from aspirin alone based on indirect comparison, and the combination was inferior to adjusted-dose warfarin. Direct randomized comparison of clopidogrel plus aspirin versus aspirin alone is ongoing in the ACTIVE-A trial [4], with results anticipated in late 2008.

The Birmingham (UK) Atrial Fibrillation Treatment in the Aged (BAFTA) trial comparing adjusted-dose warfarin (target INR range 2–3) with aspirin (75 mg daily) was carried-out in a general practice setting and restricted to atrial fibrillation patients at least 80 years old (mean age of the 973 participants at entry was 84.5 years). The positive results for protection against stroke (relative risk reduction 47%, 95%CI 19%, 66%) and remarkable safety extends the benefits of anticoagulation to octogenarians treated by general doctors using hospital anticoagulation clinics. Of note, the overall stroke rate during aspirin therapy averaged 5% per year among these very elderly patients, and consequently the number-needed-to-treat with warfarin instead of aspirin for 1 year to prevent one stroke was 43 [2].

At present, adjusted-dose warfarin remains the most efficacious prophylaxis for atrial fibrillation patients at moderate-to-high risk of stroke. Many atrial fibrillation patients have relatively low risks of stroke, and the absolute benefits of anticoagulation are modest.

Novel anticoagulants

The oral thrombin inhibitor ximelagatran appears to offer an effective alternative to adjusted-dose warfarin for stroke prevention [5, 6]. Based on results from 7,458 atrial fibrillation patients randomized in three recent trials and predicted to be at moderate-to-high risk, an average stroke risk of about 2% per year during anticoagulation occurred and all stroke was reduced by 8% (95%CI-38%, 38%) in those assigned ximelagatran 36 mg twice daily (Table 1) [1]. Assuming the extreme limit of the 95% confidence interval favoring warfarin, 130 patients would need to be treated with warfarin instead of ximelagatran for 1 year to prevent one stroke (i.e. clinically equivalent, in our view). Because the stroke rate was lower than anticipated in the ximelagatran trials, concern about efficacy for the highest-risk atrial fibrillation patients persisted, and a recent publication is relevant [7]. Among the 1,539 participants with prior stroke/TIA included in the two large ximelagatran trials, ischemic strokes occurred in 30 (2.6% per year) assigned to ximelagatran vs. 31 (2.8% per year) assigned to adjusted dose-warfarin (mean achieved INR = 2.4, 67% of exposure in the INR 2–3 target range) [7]. Ximelagatran does not require regular coagulation monitoring, but hepatotoxicity prompted its withdrawal by the manufacturer. These results, however, offer proof-of-principle that novel thrombin inhibitors can potentially provide stroke protection that is comparable to adjusted-dose warfarin with similar bleeding toxicity. Other direct thrombin inhibitors (e.g. dabigatran) are currently being tested in atrial fibrillation patients, as well as several oral factor Xa inhibitors (e.g. rivaroxaban and apixaban).

A particular challenge when comparing novel anticoagulants to adjusted-dose warfarin in randomized trials using an equivalence design has been to select the correct dose of the novel agent based either on limited phase II studies or on trials carried-out for prevention of deep venous thrombosis in younger cohorts. In contrast, management of warfarin anticoagulation has been fine-tuned over 50 years of experience in scores of clinical studies.

Table 1 Metanalyses of randomized trials of antithrombotic therapies for atrial fibrillation[a]

Comparison	Number of trials	Number of participants	Relative risk reduction of all stroke[b] (95%CI)
Adjusted-dose warfarin versus control	6	2,900	64% (49,74)
Antiplatelet agents versus control	8	4,876	22% (6,35)
Adjusted-dose warfarin versus antiplatelet agents[c]	12	12,721	39% (27,49)
Ximelagatran versus adjusted-dose warfarin	3	7,458	8% (–38,38)

CI = confidence interval

[a] Adapted from Hart et al. [1]; based intention-to-treat analysis and random effects models

[b] All stroke includes ischemic stroke and all types of intracranial hemorrhage

[c] Excludes trials comparing adjusted-dose warfarin to antiplatelet agents plus low-dose warfarin

For a new agent to show equivalence to warfarin, it requires that the agent either has a broad therapeutic window or good luck in choosing the correct dosage. An alternative design option is to compare the novel agent with aspirin in a lower risk cohort of atrial fibrillation patients, since superiority to aspirin should be theoretically easy to demonstrate with any reasonable dosage of anticoagulant. Such trials are feasible (e.g. ACTIVE-A) [4], but the likelihood of showing increased bleeding with the novel anticoagulant and uncertain efficacy compared to adjusted-dose warfarin for the large number of warfarin-eligible, higher-risk patients has made this approach less attractive. Nevertheless, in our view, the great unmet need in stroke prevention for atrial fibrillation patients remains for agents that are more efficacious than aspirin and that are easier to administer and safer than warfarin.

Optimal intensity of warfarin anticoagulation for elderly atrial fibrillation patients

The optimal anticoagulation intensity for primary prevention of stroke (and death) in elderly atrial fibrillation patients appears to be INRs between 2.0 and 2.5 (Fig. 1) [8]. There is a general misimpression that INRs between 1.6 and 1.9 do not offer substantial protection against stroke for atrial fibrillation patients. Results of the four available studies are consistent that achieved INRs of 1.6–1.9 provide 80–90% of the protection against stroke afforded by more intensive anticoagulation (Fig. 2) [9–12]. The steep slopes of the intensity-efficacy curves are notable: there is rapid decline in efficacy with INRs below 1.6 (Fig. 2). Indirect comparisons of relative risk reductions from randomized clinical trials show that mean achieved INRs of about 2.0 are associated with the greatest efficacy,

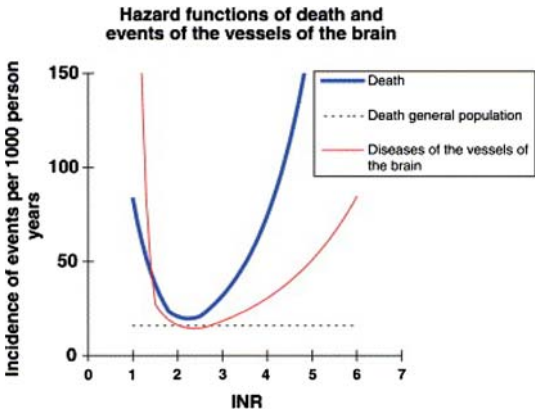

Fig. 1 Relationship between INR and death and events of vessels of the brain in the 21,967 Swedes with atrial fibrillation. The nadir of the U-shaped curves occurred at 2.2 for death and 2.4 for cerebral vascular events. From Oden et al. [8] with permission

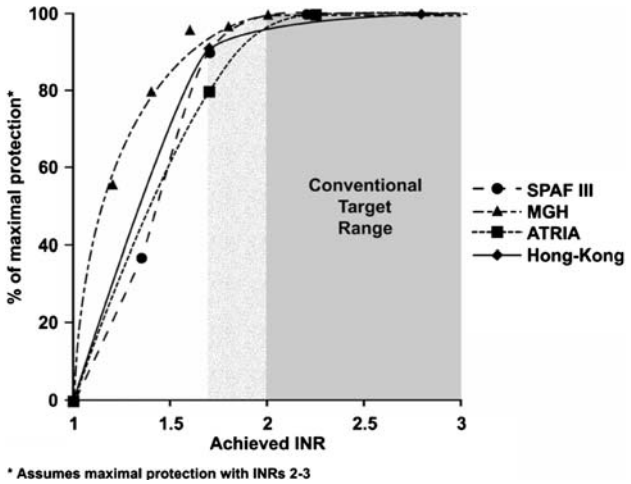

Fig. 2 Relationship between achieved INRs and ischemic stroke rates in four studies: Stroke Prevention in Atrial Fibrillation (SPAF) III clinical trial [9], Massachusetts General Hospital (MGH) case–control series [11], Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) prospective cohort [12], and Hong-Kong series [10]. From Hart RG, Individualizing antithrombotic therapy to prevent stroke in patients with atrial fibrillation in Rothwell PM (ed), *Treating Individuals*, Elsevier Limited (Oxford, United Kingdom), 2007 with permission

although this observation is limited by estimations of achieved INRs in early clinical trials using prothrombin time ratios and relatively wide confidence intervals around the point estimates of efficacy (Table 2) [13–17].

The absolute rate of intracerebral hemorrhage, the most feared complication of anticoagulation, appears to rise sharply in elderly atrial fibrillation patients when INRs exceed 3.5 [12, 18]. The optimal target INR range for anticoagulation intensity for primary stroke prevention in elderly atrial fibrillation patients appears to be slightly lower than generally recommended: 1.8–2.8 (aiming for 2.3) instead of 2.0–3.0 (aiming for 2.5), in our view. A wider extended target range of 1.6–3.0 (still aiming for 2.3) should provide high efficacy and result in fewer dosage adjustments. Available data are fewer for secondary prevention; in the two largest trials, mean achieved INRs of 2.5 and 2.9 were highly efficacious [9, 19, 20]. Current management guidelines generally advocate a target INR of 2.5 (range of 2.0–3.0) except in Japan, where lower ranges are often recommended.

Given the real-life fluctuations in anticoagulation intensity, is it better to be a little high or a little low? Very elderly atrial fibrillation patients (>75 years old) have higher rates of major bleeding during anticoagulation, but also higher rates of ischemic stroke if not anticoagulated, and age should not be a reason to withhold anticoagulation from high-risk atrial fibrillation patients [2]. For *primary prevention* in those over age 75 years (for whom the lowest efficacious intensity of anticoagulation is particularly

Table 2 Achieved INRs and stroke prevention in five primary prevention trials[a]

Trial	Number of participants	Prothrombin time ratio (PTR) target	INR target[b]	Mean achieved INR[b]	Relative risk reduction in all stroke (95%CI)
CAFA (16)	378	–	2.0–3.0	2.4	33% (–92,77)
AFASAK I (13)	671	–	2.8–4.2	2.5[c]	54% (–3,80)
SPAF I (15)	421	1.3–1.8	(2.0–4.5)	(2.6)	60% (6,83)
SPINAF (17)	571	1.2–1.5	(1.4–2.8)	(2.0)	70% (30,88)
BAATAF (14)	420	1.2–1.5	(1.5–2.7)	(2.1)	78% (23,94)

[a] Each trial included a few patients (about 6% of the overall total) with prior stroke or transient ischemic attack. Stroke outcomes include all ischemic strokes and intracranial hemorrhage by intention-to-treat analysis (see Hart et al. [1] for raw data)

[b] If in parenthesis, estimated from prothrombin time ratios that were used in the trial

[c] Estimated from the distribution of reported INRs

important to minimize bleeding), a slightly lower target INR may be reasonable considering efficacy and risk. A recent prominent guideline cautiously advocates (with methodologic caveats): "In patients over 75 years old at increased risk of bleeding and in other patients with moderate risk factors…who are unable to safely tolerate [INRs 2–3], a lower INR target of 2 (range 1.6–2.5) may be considered for primary prevention"(level of evidence C, class IIb)[21]. As described above, the recently published BAFTA showed high efficacy and reassuring safety of adjusted-dose warfarin with a target INR of 2–3 in octogenarians [2].

In summary, the optimal INR for prevention of stroke for most atrial fibrillation patients may well be slightly lower than generally recommended, but this difference is too small to practically matter considering individual patient management. INRs of 1.6–1.9 provide substantial protection, 80–90% of that afforded by higher intensities (but with a rapid fall-off below 1.6). However, it seems sensible in current clinical practice to adhere to the target INR range of 2–3 advocated by most guidelines pending additional data.

Good control of hypertension reduces warfarin-associated intracerebral hemorrhage

Predictors of CNS bleeding during warfarin anticoagulation have been defined and previously reviewed [22], and here we focus on the most treatable of these factors: hypertension (Table 3). Reduction in systolic blood pressure by 12 mmHg resulted in a 76% (95%CI 55%, 87%) reduction in intracerebral hemorrhage in the randomized PROGRESS trial involving patients with prior stroke/TIA, most taking aspirin [23]. In a subgroup analysis of 476 PROGRESS participants with atrial fibrillation (half taking anticoagulants), stroke was reduced 34% (95%CI-13%) and all major vascular events 38% (95%CI 6%, 59%) by lowering systolic blood pressure 7 mmHg [24]. Treatment

Table 3 Predictors of CNS Bleeding during Warfarin Anticoagulation

- Advancing age (≥75 years)
- Hypertension (especially systolic blood pressure ≥ 160 mmHg)
- History of cerebrovascular disease
- Intensity of anticoagulation
- Concomitant aspirin use
- "Leukoariosis" (white matter hyperdensities/hyperintensities) by CT/MRI*
- "Microbleeds" by gradient T2 MRI*

* Standardized assessment/acquistion with specificity/sensitivity has not sufficiently characterized to date to permit application to care of individual patients

of hypertension reduces the risk of ischemic stroke, as well as CNS bleeding, in atrial fibrillation patients. Good control of hypertension in recent clinical trials probably explains the unexpectedly low stroke rates observed during antiplatelet therapies [3]. Anticoagulation of elderly atrial fibrillation patients should come with a commitment to control blood pressure.

Treatment of warfarin-associated intracerebral hemorrhage

Wider use of oral anticoagulants in the elderly, particularly those with atrial fibrillation, has led to an increase in warfarin-associated intracerebral hemorrhage [25]. We conservatively estimate that about 3,000 "extra" intracerebral hemorrhages occur in the US annually due to warfarin anticoagulation [22]. About half of patients suffering this iatrogenic complication die within 30 days—a mortality rate that has been stable over the past two decades [26]. The risk of warfarin-associated CNS bleeding is directly related to the degree of INR prolongation, but most occur when the INR is in the conventional therapeutic range of 2–3 [12, 18]. In contrast to spontaneous intracerebral hemorrhage, the period of active bleeding in

anticoagulated patients is generally more prolonged, with hemorrhages slowly expanding in size for 12–24 h in many patients, offering the opportunity for intervention before brain herniation (Fig. 3) [27]. The single randomized trial testing therapies to reverse anticoagulation involved only five patients, and hence it is un-interpretable [28]. We regard warfarin-related intracerebral hemorrhage a medical emergency requiring reversal of the coagulation abnormality in order to minimize hematoma expansion. However, there are no persuasive data that urgent reversal improves clinical outcome [29], and optimal treatment remains to be defined.

Management of warfarin-associated intracerebral hemorrhage includes several options to reverse anticoagulation (Table 4) [26, 30]. In the absence of adequate clinical trials to guide acute treatment, we recently elicited the opinions of seven experts with experience treating this disorder, selected to reflect a range of subspecialties (hematology, clinical stroke, neuro-intensive care) and of geography (US, Europe, and Japan). These experts were provided with a comprehensive literature review and asked to address the question "How should anticoagulation be reversed in a non-comatose patient with acute (within 6 h of symptom onset) warfarin-associated intracerebral hemorrhage with an INR of 2.5?" [24]. Independent opinions were sought to define the range of reasonable management; no attempt at consensus was attempted, as consensus not founded on a solid evidence-based was deemed of dubious value.

All recommended administration of intravenous vitamin K. Recombinant factor VIIa was recommended as initial therapy by one expert, while another favored use of factor VIIa given with fresh frozen plasma (FFP) (Table 5). Two recommended FFP infusion, with one of these favoring factor VIIa if the patient was rapidly deteriorating. Three recommended prothrombin complex concentrate infusion as initial therapy. The potential problem associated with rapid infusion of adequate volumes of FFP alone to reverse anticoagulation was a general concern. Selected excerpts from their responses elucidate their rationales [24]:

- "Vitamin K is not a treatment alternative but an adjunctive therapy, because it does not act fast enough".
- "At present, factor VIIa should not be given outside the context of a clinical trial given uncertainties in dosing, efficacy, and whether INR correction by itself is meaningful in factor VIIa treated patients".
- "The risk of thrombosis due to the underlying indication for anticoagulation is of concern, but should not take precedence over the life-threatening effects of an ICH" [in support of factor VIIa use].
- "In absence of randomized clinical trials, but based on my own experience and biological rationale, my preference is to use factor VIIa as the treatment of choice for patients with an ICH in the setting of warfarin therapy".
- "Prothrombin complex concentrates plus vitamin K would be the first choice. Most compelling arguments pro: wide clinical experience of its use, monitoring of reversal possible. Risks/benefits of factor VIIa are as yet uncertain and monitoring is not possible".

In summary, a wide range of options for the acute treatment of warfarin-associated intracerebral hemorrhage was solicited from the seven experts, emphasizing the current uncertainties of management as reflected in recent guidelines [31]. Randomized trials have been called for and, of course, would be highly desirable, but their design and execution would be daunting and the likelihood of novel anticoagulants supplanting warfarin in the not distant future

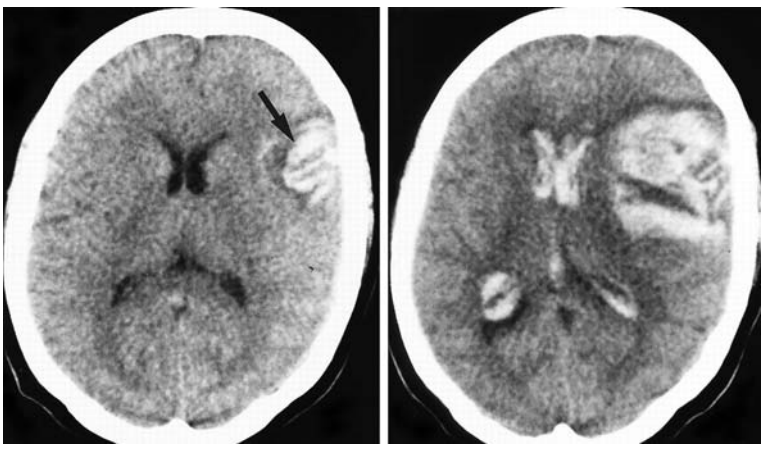

Fig. 3 Expansion of warfarin-associated intracerebral hemorrhage in a 31-year-old woman causing fatal brain herniation. Alert with headache and nonfluent aphasia, 2 h after symptom onset, INR = 2.6; arrow points at a cortical hemorrhage of the left frontal lobe (left). Coma 6 h later while awaiting infusion of fresh frozen plasma, with repeat CT showing enlargement of hemorrhage, rupture into the ventricular system, and midline shift. From Hart et al. [27], with permission

Table 4 Options for reversing anticoagulation in warfarin-associated intracerebral hemorrhage

Treatment	Time to anticoagulation reversal	Comments and cautions
Discontinuing warfarin	5–14 days	
Vitamin K[a]	6–24 h to correct the INR	Factors IX and X not repleted for even longer; Small risk of anaphylaxis with IV injection
Fresh frozen plasma (FFP)	3–6 h for infusion; typically 12–24 h for reversa	Large volume (2–6 l) can be prohibitive; thawing/type and cross-match delays initiation[b]
Prothrombin complex concentrate (PCC)	INR normal 15 min after 10 min to 1 h infusion	Limited availability, costly, variable clotting factor content based on manufacturer, potentially prothrombogenic
Factor VIIa concentrate	INR normal 15 min after bolus infusion	Short-half life, very costly, potentially prothrombogenic: although INR is normalized, unclear effect on hemostasis in absence of repletion of other clotting factors

Adapted from Aguilar et al. [26]

[a] 10 mg intravenously by slow infusion over 10 min

[b] Time from CT diagnosis of intracerebral hemorrhage to initiation of FFP averaged 111 min at one tertiary care hospital with considerable experience in treatment of the disorder [27]

Table 5 Treatment of acute warfarin-associated intracerebral hemorrhage: summary of expert opinions

	Factor VIIa	Prothrombin complex concentrate	Fresh frozen plasma	Vitamin K
#1	X			X
#2	(X)[a]		X	X
#3[b]	X		X	X
#4[b]			X	X
#5[b]		X		X
#6		X		X
#7		X		X

Adapted from Aguilar et al. [26]

[a] If rapidly deteriorating, otherwise fresh frozen plasma

[b] Served previously as a consultant to NovoNordisk, the manufacturer of recombinant factor VIIa

tempers enthusiasm. For now, focusing on prevention (particularly blood pressure control) seems a better opportunity than attempting to define optimal management [22].

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