



REGULAR ARTILCE

# Optimal INR for prevention of stroke and death in atrial fibrillation: a critical appraisal

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## Abstract

*Introduction:* Patients with nonvalvular atrial fibrillation are at increased risk for systemic embolism, predominantly disabling stroke. To study how stroke and mortality rates vary with different degrees of anticoagulation reflected by the international normalised ratio (INR) we critically assess information from different sources.

*Materials and methods:*

1. Computerized search of the medical literature published between 1980 and July 2004 was performed using MEDLINE applied to various combinations of the search terms of atrial fibrillation, warfarin, anticoagulation, anticoagulation intensity, and INR, not restricted by language.
2. We performed a record linkage analysis with death hazard estimated as a continuous function of INR based on 21,967 patients. Similarly the risk of admission to hospital or death due to diseases of the vessels of the brain was estimated.
3. Re-analysis of data earlier published by Hylek et al. from year 2003.

*Results and conclusions:*

1. One randomised study showed a significantly lower risk of stroke for mean INR 2.4 compared to mean INR 1.3 combined with aspirin. Remaining studies found INRs of 2–2.5 to be as efficacious as higher anticoagulation intensities.

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2. Mortality as well as risk of admission to hospital or death due to diseases of the vessels of the brain followed U-shaped curves with minimum at INR 2.2 and 2.4, respectively. At high INR the risk increased 2.3 times per 1 unit increase of INR for death and 1.7 times for events in the vessels of the brain.
3. The re-analysing of data of Hylek et al. indicated that there might be a substantial increase of the risk of intracranial hemorrhage when INR is increased from 2.5 to 4.

We conclude that INRs in the interval 2.0–2.5 give the lowest risk of stroke and death in patients with nonvalvular atrial fibrillation.

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## Introduction

Patients with nonvalvular atrial fibrillation are at increased risk for systemic embolism, predominantly disabling stroke. Chronic prophylaxis using oral vitamin K antagonists (VKA) greatly reduces this complication, but there is a risk of death and severe bleeding during the treatment. The intensity of anticoagulation is difficult to control and must be checked regularly. Debate continues about the optimal intensity of anticoagulation calculated from the prothrombin time and expressed as the international normalized ratio (INR). Most current guidelines recommend an INR target of 2.5 (target range 2–3) [1]. Here, we report a systematic review of published studies relating the intensity of anticoagulation to stroke and mortality, mortality correlates from computerized anticoagulation centers in Sweden, and re-analysis of data earlier published by Hylek et al. [2]. We conclude that a moderate anticoagulation intensity with INRs between 2.0 and 2.5 appears to provide optimal protection from stroke and death in patients with nonvalvular atrial fibrillation.

## Methods

### Literature review

Computerized search of the medical literature published between 1980 and July 2004 was performed using MEDLINE applied to various combinations of the search terms of atrial fibrillation, warfarin, anticoagulation, anticoagulation intensity, and International Normalized Ratio (INR), not restricted by language. Reference lists of recent review articles were also searched. Included studies were those relating different achieved INR level to stroke or death in patients with nonvalvular atrial fibrillation. The relationship of anticoagula-

tion intensity to extracranial bleeding was not considered. Studies reported in abstract only and those in which nonvalvular atrial fibrillation patients were combined with patients with prosthetic cardiac valves were excluded [3,4]. Randomized comparisons of two oral anticoagulation regimens in which the mean INR was not prolonged to  $\geq 1.2$  in both arms were not included [5,6]. Randomized comparisons in which aspirin was combined with the low-intensity anticoagulation were considered (e.g. Stroke Prevention in Atrial Fibrillation Investigators 1996) [7]. Whether the anticoagulation was given for primary prevention (i.e. no prior ischemic stroke or transient ischemic attack (TIA)) vs. secondary prevention was recorded (Table 1).

### Swedish anticoagulation clinic data

Data were obtained from hospital based and centralized anticoagulation clinics in Sweden during the year 2000. The methods of data collection were approved by the Ethics Committee for Medical Research at the University of Göteborg and have earlier been described in detail [8]. For the present study we considered an extended material compared to previously published data but now restricted to patients with nonvalvular atrial fibrillation. The material was linked with data from the register of causes of death and the register of hospitalized patients maintained by the Swedish National Board of Health and Welfare.

Each patient was followed from one INR measurement to the next one or to death if that occurred within 7 weeks. After this time, which is a common maximum interval between anticoagulant doses, we censored the patient data until a new INR measurement was performed, which was then used as a starting value for another period of surveillance. Thus, a large number of INR measurements were used as current INR values for the estimation of the death hazard function

**Table 1** Anticoagulation intensity vs. stroke in nonvalvular atrial fibrillation patients

Study type	N <sup>a</sup>	Study population	Type	Mean age (year)	Main findings
<i>Randomized comparisons</i>					
Yamaguchi et al. [10]	3/1 (115)	Japanese with recent stroke/TIA	S	67	Mean INR 1.9 (2 strokes) vs. mean INR 2.3 (2 strokes), <i>p</i> =NS.
SPAF III trial [7]	54/8 (1044)	Selected high-risk	P+S	72	Mean INR 1.3 plus aspirin (48 strokes) vs. mean INR 2.4 (14 strokes), <i>p</i> <0.001.
PATAF trial [11]	6/1 (253)	Participants from Dutch general practices	P	70	Mean INR 1.4 (4 strokes) vs. mean INR 3.1 (3 strokes), <i>p</i> =NS.
<i>Case series<sup>b</sup></i>					
SPAF III cohort [20]	54/— (1044)	High-risk cohort from a randomized trial	P+S	72	Risk of ischemic stroke equal with INRs 1.9–2.4 vs. >2.5.
Hylek et al. [2] <sup>c</sup>	141/59 (6320)	HMO cohort	P+S	71	Lowest stroke rate with INR 2.0–2.5; no increase in CNS hemorrhage if INR<4.0.
EAFT [21]	11/1 (225)	Randomized trial cohort with prior stroke/TIA	S	71	Of 38 ischemic and bleeding events, only 12 were strokes; authors concluded that the optimal intensity for secondary prevention INRs 2.0–3.9.
Nozawa et al. [22]	6/0 (156)	Prospective cohort of anticoagulated AF patients	P+S	68	Too few strokes for meaningful analysis.
Yasaka et al. [23]	11/3 (203)	Two Japanese cohorts of AF patients with prior stroke/TIA	S	68	Authors concluded that INRs of 1.6–2.6 were optimal.
<i>Case–control studies</i>					
Hylek et al. [13]	74/— (296)	Stroke cases matched with anticoagulation clinic controls	P+S	~75	Lowest odds of ischemic stroke with INRs≥2.0 and no substantial increase of risk at higher INR.

AF=atrial fibrillation; P=primary prevention; S=secondary prevention; NS=not statistically significant at *p*<0.05; HMO=health maintenance organization; SPAF=Stroke Prevention in Atrial Fibrillation; EAFT=European Atrial Fibrillation Trial; PATAF=Prevention of Arterial Thromboembolism in Atrial Fibrillation.

<sup>a</sup> Number of ischemic strokes/number of primary CNS hemorrhages; total number of anticoagulated patients given in parentheses.

<sup>b</sup> Studies derived from randomized trials in which the assessment of anticoagulation intensity was not a randomized comparison are considered as case series (e.g. SPAF).

<sup>c</sup> Number of patients and mean patient age derived from a companion publication: Go et al. [24]: 11% had prior ischemic stroke.

depending on age, sex, and INR. The function was estimated by a Poisson model earlier described [8]. Similarly we estimated the hazard function of admission to hospital or death due to diseases of the vessels of the brain (ICD 9: 430–439 and ICD 10: I60–I69). The four first INR measurements after start of treatment were excluded from analysis. The hazard functions were applied to the shift of INR distribution realized during 1996 in the Netherlands [3].

### Reanalysis of the data of Hylek et al.

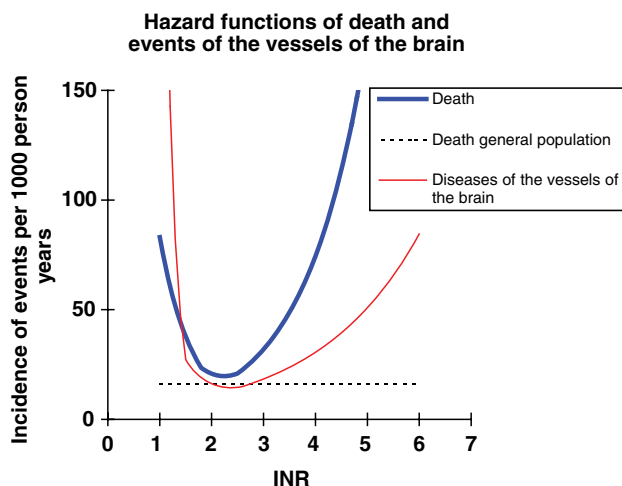
Recalculation of the recently published data presented by Hylek et al. [2] was performed. By using the data presented in Table 5 of their report, we estimated the hazard functions of ischemic stroke and of intracranial hemorrhage under monotone restrictions [9] in order to partially

eliminate potential large random fluctuations. The estimation method resulted in a hazard function, which was non-decreasing in the studied interval of INR.

## Results

### Literature review

We identified eight studies addressing the intensity of anticoagulation vs. stroke in patients with nonvalvular atrial fibrillation originating from Japan (*n*=3), North America (*n*=3), and Europe (*n*=2; Table 1). Three were randomized trials, four were case series, and one was a case-control study. The average age of atrial fibrillation patients included in these studies was 71 years (range 67 to 75 years).

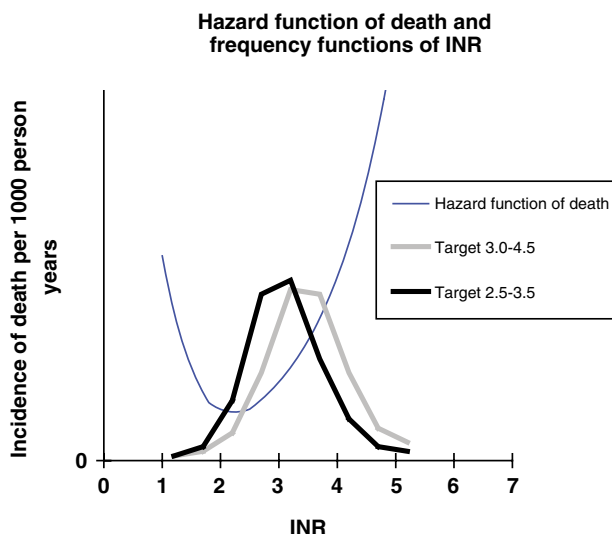


**Figure 1** The U-shaped curves were determined by use of the beta coefficients from Poisson's regression models (not shown). In this example, we assumed that the age=71 years and sex=woman. Minimum was attained at 2.24 and 2.38, respectively. The dotted horizontal line gives the death hazard for a woman at the age 71 from the general population.

Of the three randomized trials, those of Yamaguchi [10] and the PATAF trial [11] were too small to admit any conclusions (the total number of strokes in the two studies combined was 11). The Stroke Prevention in Atrial Fibrillation III trial [7] found adjusted-dose warfarin with a mean achieved INR of 2.4 superior to fixed low-dose warfarin plus aspirin with a mean achieved INR of 1.3 ( $p < 0.001$ ).

Assessment of anticoagulation intensity correlations in the case series used the time-dependent methods described by Rosendaal et al. [12]. Two cases series [2,13] analyzed all INR exposures  $< 2.0$

together, although data for INRs of 1.6–2.0 were provided by Hylek et al. from 2003 [2] and are considered in more detail in the section concerning recalculation of study results (below). In cohort analysis of the Stroke Prevention in Atrial Fibrillation III trial, which included 54 ischemic strokes, the participants with INRs between 1.9–2.4 had the same stroke rate as those with INRs  $> 2.5$ . In the case–control study by Hylek et al. from 1996 [13], maximal protection against ischemic stroke was seen with INRs  $> 2.0$  and there was no substantial increase of the risk at higher INRs (Table 1).



**Figure 2** In the Netherlands there was a change of target INR during 1996 from the interval 3.0–4.5 to 2.5–3.5 for patients with atrial fibrillation [3]. The corresponding change of distribution of INR is illustrated. When we applied the estimated hazard function of death from the Swedish material to calculate the reduction of risk after shifting from high to less high target, the resulting risk reduction was 24%.

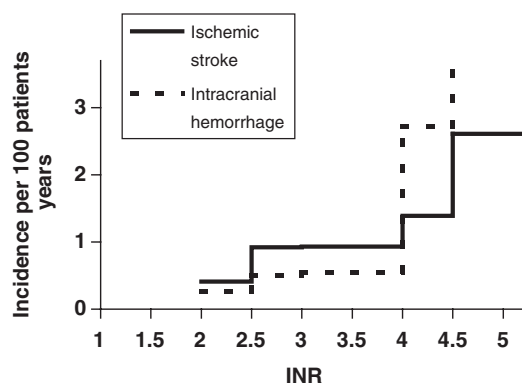
## Mortality and diseases of the vessels of the brain

For the estimation of the risk of death depending on age, sex and INR 21967 patients contributed. The mean age at start of follow up was 70.8 years. The proportion of women was 39%. There were 35780.9 patient years and 2039 deaths. The number of admissions to hospital or deaths due to diseases of the vessels of the brain was 681. Besides atrial fibrillation, 16.2% had also previous stroke or TIA as indications for treatment. Fig. 1 demonstrates U-shaped relationships between INR and the risk of death and the risk of events due to the vessels of the brain. The risks were declined associated with increasing INRs to the minimum attained at INR=2.24 for death and at INR=2.38 for the events of the vessels of the brain. For higher values of INR both hazard functions were increasing. Above INR 2.6 the estimated increase of risk per 1 unit increase of INR was 2.33 (95% confidence interval: 2.22–2.46) for death and 1.66 (95% CI: 1.41–1.96) for the events of the vessels of the brain. The mean incidence of death taken over all INR values for the warfarin treated patients in Fig. 1 corresponds to the INR values 1.7 and 2.8, which both give the incidence 27 per 1000 person years. The incidence of the general population in the example (women at the age of 71) is 16, dotted line.

In the study of Torn et al. there was a change of target INR during 1996 from the interval 3.0–4.5 to 2.5–3.5 for patients with atrial fibrillation. The corresponding change of distribution of INR is illustrated in Fig. 2. Their study also included patients with mechanical heart valves and cerebral ischemia and the shift of distribution of INR was similar as for those with atrial fibrillation. The number of patients in the last mentioned group was 3217 and in the two other groups 1380. There was a reduction of the risk of bleedings and thromboembolism of 40% (95% CI: 10–50%) after the shift of INR distribution in the total material. When we applied the estimated hazard function of death to calculate the reduction of risk when shifting from high to less high target, the calculated risk reduction was 24%. For diseases of the vessels of the brain the calculated risk reduction was 14%.

### Reanalysis of the data of Hylek et al. (2003)

In a large cohort of atrial fibrillation patients, Hylek et al. [2] reported the number of ischemic strokes and intracranial hemorrhages associated with the INR interval 2.0–2.5 to be 22 and 14,



**Figure 3** Rates of ischemic stroke and intracranial hemorrhage recalculated from the data of Hylek et al. [2]. Hazard functions of ischemic stroke and intracranial hemorrhage estimated under monotone restrictions.

respectively, and 1 of each type in the interval 3.6–3.9. Estimating the hazard functions of ischemic stroke and of intracranial hemorrhage under monotone restrictions, compared to the interval 2.0–2.5, higher INR intervals had more than double the estimated risk of ischemic stroke and intracranial hemorrhage (Fig. 3).

## Discussion

The available evidence considered here suggests that moderate anticoagulation intensities with INRs between 2.0 and 2.5 appear to provide optimal protection from stroke and death in patients with nonvalvular atrial fibrillation. However, it was not the aim of this study to suggest an algorithm or a rule for the dose adjusting of warfarin for patients with atrial fibrillation, but just to investigate the theoretical base for such rules. During monitoring of anticoagulation intensity, the possibilities of keeping INR within a narrow interval by dose adjustments are limited, contributing to the difficulty in the design of randomised studies to assess the effect of different intensities of anticoagulation. The means of the distributions are important characterisations as well as the standard deviation and the whole shape of the tails of the corresponding frequency functions. With the mentioned difficulties in mind it is not surprising that only three randomised studies comparing different algorithms are available. From these three trials, no solid evidence that a certain value or an interval of INR would be better than another, except that a mean INR of 1.3 is less efficacious than 2.4. Considering the large sample size needed for such trials, it is unlikely that additional randomised studies comparing different anticoagulation intensities will be performed.

Hence, analyses such as those considered here will remain the basis of treatment recommendations.

The expected change of INR depends on test frequency [14], previous variation, age, sex and the amount of the change of dose. Other factors, like diet, are important but they are in general out of doctor's control. If the doctor strives for an INR of say 2.2, the distribution will be different depending on the method of reaching the target. Of course it is desirable that very large randomised studies will be performed in order to compare different strategies of controlling INR with respect to stroke, thromboembolism, and with respect to death for any reason.

The study by Hylek et al. [2] was reanalyzed with the risk at high INR estimated under order restriction. The conclusion is different from that presented in their article; we calculate the stroke risk to be increasing substantially already after INR 2.5. The data presented by Hylek et al. [2] thus support that INR of 3 or higher may be more dangerous than INR 2.2–2.3 where the risk was found to be lowest.

In the analysis based on Swedish anticoagulation clinic data [8], the unexpected finding was that not only the risk of dying from bleeding but for other causes increased much by INR at high values. A simple explanation could be that diseased patients have a tendency to spontaneous increase of INR. However, the increase of risk was more pronounced for patients who had an increase of the dose compared to those who have reached the same high value of INR without increase of the dose (spontaneously). Koo et al. [15] found that patients with major bleedings and excessive anticoagulation had a significantly higher mortality compared to patients with major bleedings but non-excessive anticoagulation. Torn et al. [3] demonstrated a reduction of the risk of thromboembolism after a decrease of INR. The three last mentioned articles indicate a still unknown mechanism of danger with high INR.

Available data consistently show substantial reduction in stroke during warfarin therapy with INRs of 1.6–1.9 in atrial fibrillation patients, albeit with less protection than for INRs >2.0. Aggregate analysis of patients with unprovoked venous thromboembolism suggest that INRs of 1.5–1.9 reduce recurrence by about 75% while INRs of 2.0–3.0 reduce this risk by 90% [16]. Among relatively young patients with venous thromboembolism (mean age in the mid-50s), anticoagulation-associated intracerebral hemorrhage is very uncommon [16,17], but its risk increases dramatically with patient age. The mean age of atrial fibrillation patients receiving warfarin is in the low-70s—nearly two decades older. Indirect comparison of results of randomized trials testing warfarin in atrial fibrillation shows the

largest relative risk reductions in trials achieving INRs in the low 2's [18]. In one double-blind randomised trial comparing adjusted-dose warfarin target INR range of 1.4–2.8 vs. placebo in atrial fibrillation patients without prior stroke or TIA, a 70% reduction in stroke was seen with a mean achieved INR estimated as ~2.1 and with 29% of patient exposure during INRs <1.4 [19].

The U-shaped relationships shown in Fig. 1 were investigated further by restricting the INRs contributing to the analysis to 1.5–4 and the resulting curves almost coincided with the curves without that restriction. Thus the curves were not driven by the extreme INR values. We chose to consider all diseases of the vessels of the brain though we would like to study stroke with a possible subdivision on bleedings and thrombotic events. Because of the uncertainty of diagnosis of diseases and causes of death with ICD 9 we decided to include all codes corresponding to diseases of the vessels of the brain.

When the INR is close to 1 then the treatment in many cases had started or restarted after a stay at hospital. The risk of dying or the risk of admission again was high. The extreme decrease at INRs close to 1 must be interpreted carefully with that in mind. To some extent we tried to reduce that problem by avoiding the first four measurements. On the other side the importance of INR may be underestimated. We used the INR at the latest measurement, which was successively exchanged when there came a new measurement. However, we did not take into account the INR level before or after the measurement. The risk was of course dependent on the whole curve (as a function of time), which was unknown to us except for the measurements with some weeks between them.

We can shortly summarize the evolution of thinking between 1996 and 2004. The study by Hylek et al. from 1996 [13] indicated that the risk of ischemic stroke was steeply decreasing for INRs 1–2 and was almost constant after that. The problem at that time was to find an INR high enough to give a reasonable efficacy with respect to ischemic stroke and the only expected trouble with higher INR was the bleedings. The same year the randomised study SPAF III demonstrated that the combination of aspirin and low dose warfarin gave a higher risk of stroke than warfarin alone with mean INR 2.4, so there was no reason to doubt the potential of warfarin. The large cohort study by Hylek et al. from 2003 [2] gave another picture of the relationship between INR and the risk of ischemic stroke compared to the case–control study from 1996, now with a substantial increase of the risk also after INR 2.5. Torn et al. [3] showed that a decrease of INR could not only save bleedings but also throm-

boembolic events. The present article as well as that by Odén and Fahlén [8] (2002) show that it is reasonable to consider death and not only stroke and bleeding events. Thus the picture is changed.

In summary, these analyses of all available data suggests that anticoagulation intensities with INRs between 2 and 2.5 offer optimal protection against stroke and death for patients with nonvalvular atrial fibrillation.

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