

## Oral anticoagulation for prevention of cardioembolic stroke in patients with atrial fibrillation: Focussing the elderly

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### Abstract

Anticoagulation therapy for thromboembolism prophylaxis in patients with atrial fibrillation (AF) is based on quality information derived from numerous randomized controlled trials but continues to be a conundrum for many physicians. Age is the most cited argument to withhold anticoagulation. Ironically, because of their higher risk of stroke, the net benefit of antithrombotic therapy may be greater in octogenarians than in younger patients. Indeed, given the risk of major bleeding there is reason to be skeptical about net benefit when warfarin is used in some elderly patients with AF. This summary reviews the risks of cardioembolic stroke and bleeding in patients with atrial fibrillation with and without oral anticoagulation and spotlights the problematic nature of anticoagulation underuse in the elderly.

### Abbreviations

AF	atrial fibrillation
INR	international normalized ratio
LAA	left atrial appendage
OAC	oral anticoagulation
SEC	spontaneous echo contrast
TIA	transitory ischemic attack
VKA	vitamin K antagonist

### Introduction

Atrial fibrillation (AF) can significantly increase morbidity and mortality. It is gaining in clinical and economic importance, being the most commonly encountered tachyarrhythmia in clinical practice [1]. As the population ages, increased numbers of subjects with this condition pose a serious and growing Public Health issue [2]. It is estimated to currently affect over 6 million patients in Europe and approximately 2.3

million in the United States, and this number continues to grow rapidly because the elderly population of today has a higher prevalence of predisposing conditions for AF such as diabetes, heart failure, hypertension and coronary heart disease [3]. The lifetime risks for development of AF are 1 in 4 for men and women 40 years of age and older [4] and after adjustment for other cardiovascular risk factors, AF related mortality increases up to 1.9-fold [5]. In Patients with AF, stroke is the most serious and life threatening complication [6]. There is a fivefold increased risk of stroke and thromboembolism with AF when compared to sinus rhythm [7]. Furthermore, AF accounts for up to one fourth of all cerebrovascular events and AF-related strokes are more frequently associated with persistent and severe disabilities compared to ischemic events attributable to vascular disease [8-10]. Treatment with vitamin K-antagonists (VKA) substantially reduces the long-term complications associated with cardioembolism [11-13] but despite its proved efficiency, this option continues to be underused, even in eligible and particularly

among elderly patients who are at the highest risk for stroke [14-16]. Evidently, a great deal of overlap exists in thrombotic stroke risk and risk of bleeding. Such overlapping risk creates a difficult management problem. Therefore, on the one hand, the patient's individual risk for stroke has to be considered prior to prescription of vitamin K-antagonists for anticoagulation. On the other hand, the risk of stroke has to be outweighed against the risk of bleeding and the burden for the patient due to the need for continuous laboratory INR monitoring. The possible interactions of oral anticoagulants with food and drugs have to be considered as well as the individual lifestyle or preferences of the patient, all this with the aim of appropriate use of antithrombotic therapy [17;18]. Given the risk of major bleeding there is reason to be skeptical about net benefit when warfarin is used in some elderly patients with AF.

### Thrombogenesis in atrial fibrillation

The absence of a regular contraction of the fibrillating atria leads to an increase of atrial pressure and dilatation, which together with hemoconcentration [19;20], endothelial dysfunction, and a prothrombotic state is the prerequisite for thrombus formation [21]. Echocardiography and autopsy studies have shown that more than 90% of all thrombi in patients with AF originating in the left atrium, form in the left atrial appendage (LAA) [22-26]. The pathogenesis of LAA thrombus formation has not been fully elucidated, but the precondition is likely to result from a hypercoagulable state explained by Virchow's triad of thrombogenesis – ie, abnormal changes of the vessel wall, blood flow, and blood constituents [27;28]. Nowadays, this is translated as follows: “Abnormal blood flow” means reduced flow up to stasis due to the lack of contraction in combination with the increase of volume and size of the LAA, “abnormal blood constituents” are represented by activated coagulation factors and platelets, and “abnormal vessel wall” in this case means structural and functional changes of endothelial or endocardial cells. Dense spontaneous echocardiographic contrast (SEC) in the left atrium and left atrial appendage arises when blood flow velocity is low and this phenomenon is an independent risk factor for stroke [26;29;30]. The density of SEC increases and LAA velocities progressively decline significantly together with the accumulation of clinical risk factors for stroke evaluated by the CHADS2 score (see below) [31]. There are various

connections between morphologic and functional changes of the left atrium and the state of activation of blood coagulation, inflammation and extracellular matrix turnover, which can be demonstrated in patients with AF and are prone to an increased risk of cardiac embolism [27].

### Risk of stroke in atrial fibrillation

The risk of stroke varies considerably among the group of patients with AF. Prior stroke/TIA, hypertension, advancing age, and diabetes are consistent independent predictors of stroke in patients with atrial fibrillation. The overall evidence of an independent predictive effect of diagnosed heart failure and/or left ventricular systolic dysfunction seems to be inconsistent [32]. There are many ways of classifying stroke risk: In a recent comparison of 12 stroke risk stratification schemes in patients with nonvalvular AF, the Stroke Risk in Atrial Fibrillation Working Group [33] identified 7 schemes that were based directly on event-rate analyses (largely been identified from non-OAC arms of clinical trials, and occasionally from cohort studies), whereas 5 resulted from expert panel consensus. The most frequently included features were prior stroke/TIA (in 100% of schemes), patient age, hypertension and diabetes mellitus. Two useful resources stand out in clinical practice: the Framingham risk score, derived by Wang and colleagues (Tab. 1) [34], and the CHADS<sub>2</sub> score published by Gage et al. (Tab. 2) [35]. Both use a five step calculation to predict the risk for stroke in patients with AF: the former considers age, gender, systolic blood pressure, diabetes, and prior stroke or TIA, each category assigned with different gradings, and predicts a 5-year stroke risk in the absence of anticoagulation. Concerning the latter, the *C* stands for recent congestive heart failure, the *H* for hypertension, the *A* for age 75 or older, the *D* for diabetes, and the *S* for prior stroke or TIA. Each category is assigned one point except stroke or TIA, which gets two due to its high association with subsequent stroke. A high score on this index correlates with a raised annual stroke rate. The CHADS<sub>2</sub> score may be easier to use but less precise [33]. Nevertheless, in daily clinical routine, these score systems are sufficient for the decision about administration of appropriate thromboprophylaxis. In some rare unclear cases, echocardiography will be useful in refining the risk [36]. In particular, transesophageal echocardiography may be used to identify the presence of left atrial SEC, which is

Table 1: The Framingham Risk Score [34]

Step 1		Step 2		Step 3		Step 4		Step 5		Pts	5-year risk (%)
Age, y	Pts	Sex	Pts	syst. blood pressure (mmHg)	Pts	Diabetes	Pts	Prior stroke/TIA	Pts		
55-59	0	Man	0	<120	0	no	0	no	0	0-1	5
60-62	1	Woman	6	120-139	1	yes	5	yes	6	2-3	6
63-66	2			140-159	2					4	7
67-71	3			160-179	3					5	8
72-74	4			>179	4					6-7	9
75-77	5									8	11
78-81	6									9	12
82-85	7									10	13
86-90	8									11	14
91-93	9									12	16
>93	10									13	18
										14	19
										15	21
										16	24
										17	26
										18	28
										19	31
										20	34
										21	37
										22	41
										23	44
										24	48
										25	51
										26	55
										27	59
										28	63
										29	67
										30	71
										31	75

Add up points from steps 1 through 5  
Look up predicted 5-year-risk of stroke in table

Table 2: The CHADS2 score (modified according to [35])

No. patients	No. strokes	stroke rate (95% CI)	CHADS <sub>2</sub> score
120	2	1,9 (1,2-3,0)	0
463	17	2,8 (2,0-3,8)	1
523	23	4,0 (3,1-5,1)	2
327	25	5,9 (4,6-7,3)	3
220	19	8,5 (6,3-11,1)	4
65	6	12,5 (8,2-17,5)	5
5	2	18,2 (10,5-27,4)	6

strongly associated with thrombus formation in the LAA and future strokes [29;30;37;38].

It is a widespread mistaken belief that paroxysmal AF has a lower stroke risk than permanent AF. In terms of the procoagulant state, patients with paroxysmal AF have the same abnormalities of haemostasis, platelet and endothelial function like those with permanent arrhythmia [20;39;40]. Hart and colleagues [41] reported a longitudinal cohort study comparing 460 participants with intermittent AF, who were compared

with 1552 with sustained AF treated with aspirin in the Stroke Prevention in Atrial Fibrillation studies. After an average of two years' follow-up, the annualized rate of ischemic stroke was similar for those with paroxysmal (3.2%) and permanent AF (3.3%). Of those predicted to be high risk, the observed stroke rate was 7.8% per year. Hohnloser et al. [42] reported a post-hoc subgroup analysis of the patients with paroxysmal AF (n = 1202) from the ACTIVE W (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) trial, comparing warfarin to combined antiplatelet therapy with aspirin and clopidogrel for the prevention of vascular events in 6706 AF patients. The annualized risk of stroke or systemic embolism was 2.0% in paroxysmal AF compared with 2.2% in persistent or permanent AF.

In the Euro Heart Survey [43], permanent AF patients were older and more often had a previous stroke, diabetes, and heart failure. As a consequence, permanent AF patients most often were at the highest risk for stroke according to the CHADS<sub>2</sub> score. Regardless of the stroke risk score, paroxysmal AF patients had a much lower chance for receiving OAC at baseline. Finally, the results indicated that risk for stroke in parox-

ysmal AF is at least comparable with that of persistent and permanent AF and potentially even higher following cardioversion. These findings strengthen the recommendation that in the presence of appropriate risk factors, clinical subtype of AF should currently not influence the decision to anticoagulate [17].

### **Oral anticoagulation for stroke prevention is effective but underused**

A series of clinical trials have shown the remarkable efficacy of anticoagulation with warfarin compared to placebo in reducing stroke risk in patients with AF (Copenhagen Atrial Fibrillation Aspirin and Anticoagulation, AFASAK [44]; Stroke Prevention in Atrial Fibrillation, SPAF [45]; Boston Area Anticoagulation Trial for Atrial Fibrillation, BAATAF [46]; Canadian Atrial Fibrillation Anticoagulation, CAFA [47]; and Stroke Prevention in Nonrheumatic Atrial Fibrillation, SPINAF [48]). In 2007, Hart and colleagues published a meta analysis [13] of the aforementioned 5 primary prevention trials plus one study of secondary prevention [49] and demonstrated a 62% relative risk reduction for stroke in patients anticoagulated with vitamin K-antagonists (warfarin). Additionally, a stroke causes higher costs than its prophylaxis, including expenses for drugs, monitoring, nursing, loss of working hours, hospital admissions and procedures due to bleeding complications [50]. Nevertheless, this effect of anticoagulant therapy depends on achieving a protective therapeutic range. Patients with AF within the recommended target INR range of 2.0-3.0 survive longer and have reduced morbidity [51] and gradually every 10% increase in time out of therapeutic range is associated with an increased risk of ischaemic stroke [52]. However, the principal problem with anticoagulation is the variability of the effect of coumarin derivatives on the hemostatic system; patients may require very different doses (up to 10-fold differences) to reach the same level of anticoagulation, and the required dose may also vary over time in an individual patient. In the studies mentioned above, a relevant number of strokes occurred among patients randomized to receive warfarin, but with subtherapeutic INR levels below 2. As the trials were designed as intention-to-treat analyses, it is likely that the real efficacy of warfarin is underestimated.

Despite the proven benefit, OAC with warfarin or other vitamin K-antagonists remains underused in clinical practice [53-57]. The review of the literature

identifies several barriers to the prescription of vitamin K-antagonists which are related to the patient, the physician, and the health care system [53]. One of the strongest patient related predictors of warfarin withholding is age. The most important physician related reasons not to anticoagulate are 1) the perception of the benefit vs risk of therapy, insofar as the risk for embolism relative to hemorrhage is judged to be lower, and 2) the relative contraindication to therapy due to the lack of patient reliability or patient noncompliance as a reason for difficulties in monitoring the prothrombin ratio. Of the 596 (64.4%) eligible family physicians who participated in a representative survey in Australia, 15.8% reported having a patient with non-valvular atrial fibrillation experience an intracranial hemorrhage with anticoagulation and 45.8% had a patient with known nonvalvular atrial fibrillation experience a stroke without anticoagulation. When presented with a patient at „very high risk“ of stroke, only 45.6% of family physicians selected warfarin in the presence of a minor falls risk and 17.1% would anticoagulate if the patient had a treated peptic ulcer. Family physicians with less decisional conflict and longer-standing practices were more likely to endorse anticoagulation [58].

Concerns about the external validity of the aforementioned trials cannot be ruled out as an argument for withholding warfarin, as they excluded most of the potential candidates, with some trials excluding >90% of screened patients [45;47;48]. The most common reasons for trial exclusion were age and relative contraindications to anticoagulation. Therefore, the results in favor of anticoagulation were obtained under ideal circumstances for patients with an average age at about 70 years. Consistently, there are physicians who are cautious with prescribing anticoagulants to patients who are older and/or frailer than the trial population [59]. Finally, concerning the health care system, there may be a lack of resources and experienced personnel in the community to adopt practice recommendations and to provide anticoagulation therapy at rates similar to those of controlled clinical trials [35]. There is no doubt that INR monitoring either through patient self-management, or by specialized anticoagulation clinics improves the quality of care and reduces the rate of complications [60-63].

Gage and colleagues [54] reported on 597 hospitalized cases with a mean age of 80 years, which had chronic AF documented during their index admission. Overall, at discharge 34% of patients were prescribed warfarin, 21% were prescribed aspirin, and 45% were

not prescribed any antithrombotic therapy. Patients aged  $\geq 76$  years were less likely to receive antithrombotic therapy than were younger patients ( $p < 0.001$ ), females were less likely than males to receive antithrombotic therapy ( $p = 0.02$ ), and patients treated in rural facilities were prescribed antithrombotic therapy less frequently than patients in metropolitan facilities ( $p = 0.02$ ). Outcome analysis in 463 cases demonstrated that patients who were prescribed antithrombotic therapy were significantly less likely to have an adverse outcome (death or hospitalization for an ischemic event;  $p = 0.0001$ ). Thirty-three suffered strokes or TIAs: 9 of these occurred in the 163 patients who were prescribed warfarin, 8 occurred in the 96 patients who were prescribed aspirin, and 16 occurred in the 204 patients who were prescribed neither therapy. The authors discussed two main reasons for the low use of antithrombotic therapy: inconvenience and physicians' fear of hemorrhage. Physicians' subjective judgement seems to attribute a greater negative value to hemorrhagic strokes than to ischemic ones, even when the health outcomes are the same. The emphasis on avoiding hemorrhagic strokes and other iatrogenic events may cause physicians and patients to choose therapy that minimizes side effects rather than therapy that maximizes benefit.

### Anticoagulation in the elderly

Due to the improvement of healthcare, education and life standard in the industrial nations, the general population is ageing and surviving well into their eighties and beyond. However, ageing is a complex process, not rarely coupled with reduced mobility and greater frailty, with a tendency to fall. These are the most cited arguments to withhold anticoagulation from the elderly [64], but with the possible consequence of devastating stroke and severe disability. Ironically, because of their higher risk of stroke, the net benefit of antithrombotic therapy may be greater in octogenarians than in younger patients [65]. Physicians' aversion to cause a hemorrhage may account for the underuse of oral VKA therapy in the very elderly because it is recognized that increasing age is a risk factor for bleeding, especially in those aged over 85 years [66–69]. Indeed, there are conditions which appear primarily in elder patients increasing the risk for overdosing warfarin with the consequence of severe bleeding: a) pharmacodynamic issues, as patients with low body weight or low serum albumin, perhaps due to malnu-

trition, may require lower doses of warfarin [70]; b) comorbid conditions like liver diseases, congestive heart failure or acute infectious diseases; and c) polypharmacy, especially in patients with self-medication of herbal compounds or unknown vitamin supplementation by caring family members [71]. Due to the higher prevalence of cardiovascular diseases, platelet inhibitors such as aspirin or clopidogrel or, recently, prasugrel are often prescribed for older patients. Concerning the latter, the TRITON–TIMI 38 study demonstrated a reduction in the risk of myocardial infarction and coronary stent thrombosis [72]. However, the elderly were one of three subgroups in this trial which appeared to be particularly prone to serious bleeding [73]. Therefore, it would be best to avoid prasugrel in such patients, especially in those who receive warfarin.

One of the most decisive factors in terms of OAC is the elderly patients' propensity to fall although the real impact of falls on morbidity including intracranial hemorrhage among patients treated with warfarin remains uncertain. Man-Son-Hing and coworkers stated that persons taking warfarin must fall about 295 times in a year before developing the most serious type of haemorrhage associated with anticoagulation, that is, subdural haematomas given that falls (1 in 10) usually cause other major injuries (i.e. fractures) and, therefore, persons who fall are much more likely to suffer other serious morbidities [74].

Recently, the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA [75], reaffirmed that warfarin is superior to ASA in stroke prevention also in an elderly population aged  $> 75$  years. On the other hand, the risk of major hemorrhage, including intracranial and hemorrhagic stroke, was similar in both the aspirin (2.0% per year) and warfarin (1.9% per year) treated patients. The authors recommended the use of anticoagulation (warfarin) for all people aged over 75 years who have atrial fibrillation, unless there are contraindications or the patient decides that the size of the benefit is not worth the inconvenience of the treatment.

### Bleeding risk under oral anticoagulation

The benefits of anticoagulation do not come without a risk, especially in the presence of comorbid conditions like recent intracerebral or gastrointestinal hemorrhage or, stroke, uncontrolled hypertension, liver disease, cancer, and renal insufficiency [76]. The most

dangerous and, therefore, the most feared bleeding complication associated with OAC is intracranial hemorrhage [77]. Fortunately, this condition is rare, but the most common bleeding sites are the gastrointestinal or genitourinary tract [78]. Notably, bleeding phenomena can also often be seen in the microcirculation but they occur independently of the intensity of treatment and are not predictive for future clinically obvious hemorrhage [79]. A meta-analysis of six clinical trials on patients on OAC due to AF with a mean age of  $71.7 \pm 8.8$  revealed major bleeding in 2.2, hemorrhagic stroke in 0.5, or lethal bleeding in 0.4 patients per 100 patient-years [80]. The use of oral anticoagulant significantly increased the rate of major bleeding, with 15.3% of all major bleeding episodes being lethal. On the other hand, patients with a previous history of stroke or transient ischemic attack had an absolute risk reduction of 6.0% per year (number needed to treat (NNT) = 17) while those patients without previous cerebrovascular disease had an absolute risk reduction of 1.2% per year (NNT = 83) [80]. Comparably, in the Stroke Prevention in Atrial Fibrillation Trial, the rate of major bleeding in the warfarin group was 2.3% per year. However, for those younger than 75 it was 1.7% and for the elder it was 4.2% per year [81]. Hylek and coworkers [82] studied a cohort of 472 patients of whom one third was  $\geq 80$  years of age compared with a total of 20 patients  $>75$  years in the pooled analysis of the 5 randomized trials that proved efficacy of anticoagulation [13], and 91% had  $\geq 1$  stroke risk factor. The cumulative incidence of major hemorrhage for patients  $\geq 80$  years of age was 13.1 per 100 person-years and 4.7 for those  $<80$  years of age ( $P=0.009$ ). A further important finding to be emphasized from Hylek et al. is the enhanced risk of bleeding in patients while starting anticoagulation therapy. This phenomenon, although known, has been underappreciated by many clinicians. In the SPORTIF III and V trials in which the direct thrombin inhibitor ximelagatran was compared to warfarin for stroke prevention in AF, the rate of intracranial hemorrhage was 0.4%, and the rate for major hemorrhage was 2.5% per year in the warfarin group [83;84]. In a pooled analysis of patients  $\geq 75$  ( $n=2804$ ) and  $<75$  ( $n=4525$ ) years, ximelagatran was as effective as warfarin in reducing stroke/systemic emboli in the elderly (2.23%/year with ximelagatran vs 2.27%/year with warfarin) as in younger patients (1.25%/year vs 1.28%/year). Total bleeds were significantly lower with ximelagatran compared with warfarin in elderly (40% vs 45%,

$P=0.01$ ) and younger (27% vs 35%,  $P<0.001$ ) patients [85].

The results of these clinical trials also clearly indicate that the risk of bleeding depends on warfarin treatment intensity. If an INR value exceeds 4, the risk of hemorrhage is markedly increased [86;87]. Koo and coworkers reported on a cohort of patients with anticoagulation-associated hemorrhage, in which excessive anticoagulation contributed independently to increased morbidity and mortality [88]. It must be mentioned that overutilization of warfarin in patients at low risk of thrombotic stroke could be demonstrated in the Euro Heart Survey on Atrial Fibrillation and may also contribute to an increased morbidity due to anticoagulation. Even with the use of the more strict 2001 guidelines, the authors reported that 50% of AF patients without stroke risk factors were being treated with vitamin K antagonists [89].

Comparable to the existing stroke risk stratification schemes there are bleeding risk models [78;90-94]: Beyth and coworkers [90] identified four independent risk factors for bleeding: age  $\geq 65$  years, history of gastrointestinal bleeding, history of stroke, and one or more of four specific comorbid conditions. They found a cumulative incidence of major bleeding at 48 months of 53% in high-risk patients (three or four risk factors), 12% in middle-risk patients (one or two risk factors), and 3% in low-risk patients (no risk factors). Kuijer and colleagues [91] developed another prediction model based on age, gender, and the presence of malignancy. In patients classified at high, middle, and low risk, the frequency of major bleeding was 7%, 4%, and 1%, respectively, after 3 months of therapy. Comparable bleeding rates for comparable risk classes were found by Shireman and colleagues [93] (5.4%, 2.0%, and 0.9%, respectively, after 90 days of treatment) using the following criteria: age  $>70$  years; gender; remote bleeding; recent bleeding; alcohol/drug abuse; diabetes; anemia; and antiplatelet use. Gage and colleagues [94] gave 2 points for a prior bleed and 1 point for each of 10 further stroke risk factors and claimed the highest accuracy of all other bleed prediction schemes. Nevertheless, none of these risk prediction schemes has been fully validated in large prospective cohorts of AF patients.

### Future antithrombotic strategies

The difficulties of OAC treatment may also be overcome by the development of new anticoagulants that do not require regular monitoring and which have fewer drug interactions. Oral direct thrombin inhibitors include ximelagatran (now withdrawn) and dabigatran. They bind directly to thrombin, blocking its interaction with substrates and thereby preventing fibrin formation, thrombin-mediated activation of Factors V, VIII, XI, and XIII, and thrombin-induced platelet-aggregation [95]. The use of these thrombin-inhibitors confirmed the efficacy of anticoagulation for stroke prophylaxis. Ximelagatran, administered in a fixed dose without coagulation monitoring, protected high risk patients with atrial fibrillation against thromboembolism at least as effectively as well-controlled warfarin, and was associated with less bleeding [83;84]. However, safety concerns regarding increased liver toxicity led the Food and Drug Administration to reject the sponsor's application for ximelagatran [96]. Very recently, the results of a phase 3 noninferiority trial on dabigatran etexilate against warfarin in AF have been published. In patients with atrial fibrillation, dabigatran given at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage. Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage (Fig. 1) [97]. Thus, the 150-mg dose appears to be more ef-

ficacious and the 110-mg dose appears to be safer than warfarin. Remarkably, the time in therapeutic range in the warfarin group was 64% which can be compared to contemporary studies but reflects optimal study conditions.

An attractive alternative to direct thrombin inhibition is selective inhibition of FXa. Several factor Xa inhibitors are under investigation, including rivaroxaban and apixaban. The recently published RECORD studies showed that rivaroxaban was more effective than enoxaparin in preventing venous thromboembolism after total knee or hip replacement. The ROCKET-AF study is a randomized, double-blind study that will compare the efficacy and safety of rivaroxaban 20 mg once daily with warfarin for the prevention of stroke in approximately 14 000 patients with AF. A phase III study, ARISTOTLE, which investigates apixaban 5 mg bid for the prevention of stroke in patients with AF, is ongoing [98].

### Nonpharmacologic approaches

Patients at high risk of embolic stroke but with contraindications for OAC are in a need of an alternative approach that is not associated with a long-term risk of hemorrhage and other attendant circumstances. This is particularly true for those who survived intracranial hemorrhage but remain at high risk for cardiogenic embolism. The reasonable alternative may be the exclusion of the LAA cavity from circulation either by surgical or by percutaneous catheter-based procedures.

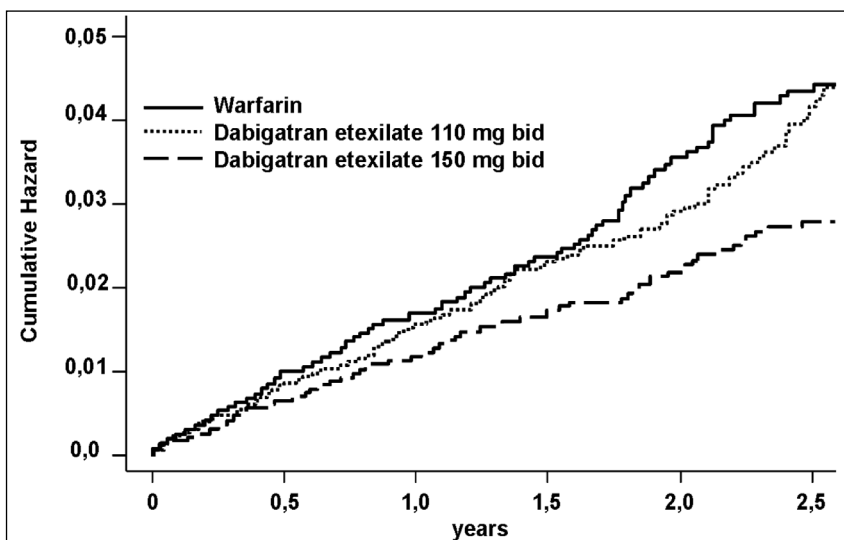


Figure 1. RE-LY-Study: Cumulative hazard rates for the primary outcome of stroke or systemic embolism (modified according to [97]).

Currently, excision of the LAA at the time of mitral valve surgery is recommended to reduce future stroke risk [99]. The efficiency of LAA exclusion in patients undergoing elective coronary artery bypass graft surgery was shown in the LAA Occlusion Study (LAAOS) [100]. Thus, based on the surgical experience, the development of a less invasive percutaneous approach to close the LAA by implantation of a mechanical device was a logical consequence [101;102]. In this issue, Park et al. give an overview on the latest developments in this field.

## Summary

With an aging population, AF is a growing public health problem with significant clinical consequences. Despite conclusive evidence from randomized controlled clinical trials, the use of OAC for the prevention of ischemic stroke in AF is suboptimal probably due to both, the real-world limitations of warfarin and the disregard for risk guided treatment. In patients with an overall risk of stroke or cardiovascular events that is substantially higher than that of major bleeding the proven absolute risk reductions of stroke cannot substantially be offset by small but statistically significant increases in major hemorrhage. Therefore, prophylaxis must be better tailored to the patient's stroke and bleeding risk profile to steer safely between the Scylla of thrombosis or embolism and the Charybdis of bleeding. Moreover, appropriate facilities to monitor INR such as anticoagulation clinics and non-pharmacological alternatives are necessary. However, there are promising new antithrombotic agents with potential benefits including fixed dosing, rapid onset of action, and no requirement for therapeutic monitoring at various stages of development and clinical evaluation. Finally, the alternative to close the left atrial appendage as the main source of cardiogenic emboli with a less invasive percutaneous procedure may help to reduce major stroke rates in the future.

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