

PREVENTION AND TREATMENT OF ISCHEMIC STROKE IN PATIENTS WITH ATRIAL FIBRILLATION

Daniela Arabadzhieva

First Clinic of Neurology, St. Marina University Hospital of Varna

ABSTRACT

Atrial fibrillation (AF) is the most common sustained arrhythmia. It affects a considerable number of patients in the world and is responsible for ischemic stroke (IS) in many of them. Age greater than 75 years, congestive heart failure, arterial hypertension, diabetes mellitus, tobacco smoking and other structural lesions of the heart represent the main risk factors for IS in AF patients. Long-term anticoagulation therapy with warfarin is considered the most effective therapy for IS prevention in selected patients with AF and other risk factors. However, management of the drug presents with some challenges such as need for frequent monitoring, interactions with food and other medications, variability in metabolism and delayed onset of action. Antiplatelet therapy may provide some benefit for patients who can't tolerate warfarin. Recently, direct oral thrombin inhibitor dabigatran and oral factor Xa inhibitors rivaroxaban and apixaban are approved by the Food and Drug Administration (FDA). Non-pharmacologic approaches to IS prevention in AF focus on occlusion or ligation of the left atrial appendage, which is often the location of thrombus formation and on percutaneous techniques that may not require anticoagulation afterwards as well. New diagnostic modalities detect paroxysmal AF and expand the potential impact of preventive strategies on the population.

Key words: *ischemic stroke, atrial fibrillation, treatment, risk factors, prevention*

SOCIAL EPIDEMIOLOGY

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice (4,35,39). AF is independently associated with a fivefold increased risk of ischemic stroke (IS). IS caused by AF is particularly severe and disabling and IS prevention is of rising significance nowadays (47), particularly in the elderly. AF presence leads to more severe initial neurological involvement,

longer hospitalization, greater disability and a lower probability of discharge to home (39).

Acute IS incidence rate is studied in Kurashiki City, Japan, between March 2009 and February 2010. Crude incidence rate for first-ever cerebral infarction per 100,000 residents is 108,8 (95% confidence interval, 99,4-118,1). Using the world population model, age-adjusted incidence rate is 38,4 (95% confidence interval, 26,3-50,5) (25).

The Argentinean National Stroke Registry prospective, country-wide, hospital-based study demonstrates that 39,5% of 726 acute IS patients are unemployed. In-hospital mortality is higher in these patients than those who are employed (12,0% versus 5,0%; $p=0,003$). On multivariate analysis, being unemployed ($p=0,005$), IS severity ($p=0,018$), and infarction size >15 mm ($p=0,019$) are related to higher in-hospital mortality rate indicating that social factors influence on poor outcomes after IS (44).

Address for correspondence:

Daniela Arabadzhieva, MD
First Clinic of Neurology,
St. Marina University Hospital of Varna
1 Hristo Smirnenski Str.,
9010 Varna, Bulgaria
e-mail: d.arabadzhieva@abv.bg

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PATHOPHYSIOLOGICAL MECHANISMS OF AF

AF causes IS by thrombus formation in the left atrial appendage (LAA) and subsequent embolism to the brain. There is a link between AF and endothelial dysfunction explaining the relationship between AF, cardiovascular risk factors and IS (24). Endothelial dysfunction is a maladaptive state of endothelial cells, characterized by a constellation of impaired physiologic responses including: poor regulation of arterial tone, increased proinflammatory and prothrombotic mediators, overexpression of adhesion molecules and impaired endothelium-dependent vasodilation (24). Experimental AF is associated with these features and additionally enhanced platelet activation (24). Endothelial dysfunction can be particularly relevant in patients with other underlying disorders, such as arterial hypertension and diabetes mellitus, and offers some explanation as to why AF patients without other risk factors (i. e. those with 'lone AF') have a low risk of IS. Levels of von Willebrand's factor are used in risk stratification for AF patients and are an independent risk factor for adverse events in them (37).

RISK FACTORS AND PROGNOSIS

Major risk factors for IS in the setting of AF include age greater than 75 years, congestive heart failure, arterial hypertension (AH), diabetes mellitus, tobacco smoking and other structural lesions of the heart (38).

The analysis of 612 IS Japanese patients (293 with lacunar infarctions, 107 with large-artery occlusive infarctions, and 168 with embolic infarctions) indicates excess risk of IS in men with serum total cholesterol levels of $\geq 6,21$ mmol/L than in those with the lowest category ($< 4,65$ mmol/L). Multivariate hazard ratios and 95% confidence intervals are 1,63 (1,14-2,35) for men and 1,03 (0,69-1,55) for women but concerning large-artery occlusive infarction, they are 2,86 (1,31-6,27) for men and 0,75 (0,28-2,01) for women, respectively (14).

The patients with prior IS or transient ischemic attack (TIA) and AF face the highest risk, more than twice that of AF patients without such a history. These factors are incorporated into risk stratification tools such as the commonly used CHADS2

score (C=congestive heart failure, H=history of hypertension, A=age ≥ 75 years, D=diabetes, S=prior stroke or TIA). IS or prior TIA is assigned 2 points, while the other risk factors count for 1 point each. This 0- to 6-point scale can be used to quantify the patient's risk of IS and thus guide decision making regarding the need for anticoagulation. This system is a widely used system for estimating the risk of IS in AF patients. As a CHADS2 score of 2 is accepted as the level at which anticoagulation should be administered, any patient with a history of IS or TIA automatically reaches this threshold. More modest risk factors include female gender and presence of coronary artery disease or peripheral vascular disease (29).

IS severity is assessed in 298 patients with AF-related IS using National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale scores 'at discharge' instead of the more common time of three months after onset (26). A high-risk CHADS2 score at admission is a powerful predictor of poor neurological outcome after controlling for all possible confounders and thus an independent predictor of all causes of death during the follow-up (26). Recently, however, neurological scores at discharge sufficiently represent the final neurological outcome of patients (8).

Additional risk factors include echocardiographic findings of complex aortic plaque or functional left atrial abnormalities. Age is a critical risk factor, too. Some additional factors are included in the scoring system CHA2DS2-VASc which considers the presence of vascular disease (V), age between 65 and 74 years (A) and female gender (Sc) (37). This expanded scoring system is most useful at risk-stratifying those patients at the lower end of CHADS2 spectra (48).

The relationship between AF episode duration and the risk of IS is of great interest. Though paroxysmal and persistent AF have similar IS risks, there is no clear threshold for the AF duration necessary to form a thrombus in the left atrium (38). A period of 48 hours is accepted as the period before which cardioversion can be performed without the need for prior anticoagulation or transesophageal echocardiography (TEE). However, studies of patients being continually monitored via their implanted cardiac rhythm management devices

such as pacemakers and defibrillators render this threshold questionable.

Pacemaker patients at low risk (CHADS₂=0) have a low risk of IS regardless of their AF burden (9) while patients at a high risk (CHADS₂≥3) have a high risk of IS even with no documented AF. For the intermediate-risk group, the risk of IS depends on the patient's AF burden as patients with more AF have an increased risk of IS. The comparison of traditional methods of monitoring patients for AF episodes with recordings from the implanted devices shows that occasional Holter monitoring typically done to assess AF burden is of low sensitivity and poor negative predictive value (9). The uncertainty surrounding the minimum AF duration needed to cause IS raises important questions as to the appropriate threshold for anticoagulation therapy in patients in whom the duration of AF can be reliably measured.

Current IS and bleeding risk scoring schemes in AF patients are based on complex scoring systems including similar risk factors which could confuse clinical decision making to balance these two risks and limits the applicability of these schemes. Along with physicians' fear of inducing bleeding complications it results in reduced usage of anticoagulation therapy in older patients. A pragmatic approach based on a yes/no decision rather than a risk scoring stratification unless there is a contraindication for oral anticoagulation is suggested (3).

In univariate analysis, risks such as age ≥75 years, history of cerebral ischemia, CHADS₂ score ≥2 and TEE presence significantly correlate with IS incidence rate of patients with nonvalvular AF (NVAf) (45).

AH, hyperlipidemia and tobacco smoking are identified as risk factors of new vascular events by nearly 90% of 182 surviving primary care patients with previous IS or TIA while AF and diabetes mellitus are recognized by less than 50% of these patients (43).

There are increased hazard ratios of IS among manual workers in Sweden occupationally exposed to small (<1 μm) as well as large particles (>1 μm) for ≥5 years. The risks are higher for workers exposed for ≥5 years compared to 'ever exposed' participants indicating a dose-response relationship (42).

About one half of cases with IS can be prevented through control of modifiable risk factors and lifestyle changes. Recent clinical trials of new anticoagulants (factor Xa inhibitors and direct thrombin inhibitors) indicate alternative strategies in IS prevention for AF patients (17).

A systematic review of the evidence on the relationship between the individual clinical, echocardiographic and laboratory characteristics of AF patients and the risk of IS demonstrates the following good independent predictors of IS: a prior IS or TIA (15/16 positive studies, risk ratio (RR) 2,86), AH (11/20 positive studies, RR 2,27), aging (9/13 positive studies, RR 1,46 per decade increase), structural heart disease (9/13 positive studies, RR 2,0) and diabetes mellitus (9/14 positive studies, RR 1,62) (33).

Among 1688 IS patients alive at three months, age, prestroke dependency, IS severity, and absence of comorbidities are statistically significantly associated with good functional outcome. In multivariate analysis, a higher probability of good outcome is observed in patients with college or university degree than in those with no completed education (23).

DRUG THERAPY

Initially, anticoagulation with the vitamin K antagonist warfarin represents the optimal drug for IS prevention in moderate- to high-risk AF patients. Aspirin exerts a more modest effect and reduces the risk of IS by a relative factor of 21% (38).

Warfarin therapy is complicated by interactions with food and other drugs, variability in metabolism, a delayed onset of action and requirement for regular monitoring (10). Patients who are monitored by specialized anticoagulation clinics are out of the therapeutic range about 37% of the time, and warfarin patients monitored in community-based ones do 49% of the time (6). Warfarin-associated hemorrhage results in a mortality of 42% with another 34% of patients suffering from major disability (20).

A total 1953 IS patients discontinue warfarin 3-4 days before AF ablation (first group) and 1,327 ones continue this therapy during the periprocedural period (second group). Symptomatic IS or TIA occur in 13 patients (0,67%) of the first group and in 2 patients (0,15%) of the second one (p=0,021). Major hemorrhagic complications occur in 26 patients

(1,3%) of the first group and in 15 patients (1,1%) of the second one ($p=0,80$). The continued warfarin therapy could reduce IS incidence rate without increasing the hemorrhagic complications (27).

The Rochester Epidemiology Project Medical Linkage System is used to examine 100 acute IS patients with AF on warfarin treatment for secondary IS prevention from 1980 to 1994. Major bleeding events occur in 41 patients at a median of 19 months after warfarin initiation. Patients with a history of hemorrhage before warfarin treatment develop more commonly major hemorrhage (15% versus 3%; $p=0,04$) which indicates high lifetime bleeding risk associated with warfarin treatment (40).

The risk of IS due to the use of warfarin and aspirin is estimated in a population-based cohort study of all patients aged at least 18 years with a first-ever diagnosis of chronic AF in 1993-2008 within the UK General Practice Research Database. IS is diagnosed in 5519 out of a total of 70766 AF patients. Warfarin provides a net clinical benefit maintained with longer duration of use within therapeutic range (5).

Some patients with AF and concomitant IS risk factors can be unsuitable for anticoagulation because of refusal to comply with regular international normalized ratio (INR) monitoring, fall risk or prior major hemorrhage due to an irreversible cause. The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events compares aspirin with combined aspirin and clopidogrel in patients with AF judged to be warfarin ineligible (13). The combination therapy reduces by 0,9% the absolute risk of IS and increases the risk of major bleeding (2,0% versus 1,3%). Although this result suggests that the bleeding risks of combination therapy often outweigh its benefits, this therapy can be sufficient in patients who are already receiving it following a coronary intervention, are at a lower IS risk, or are warfarin ineligible (13).

A meta-analysis of 13 randomized trials comparing the combination of clopidogrel and aspirin versus aspirin alone and covering a total of 90433 participants at a mean age 63 years shows that IS reduction by means of dual antiplatelet therapy by 23%. Among 1930 participants with recent (<30 days) brain ischemia from four trials, IS reduces by 33%

by using of clopidogrel plus aspirin when compared to aspirin alone. However, dual antiplatelet therapy enhances the risk of major bleeding by 40% (31).

Warfarin's many disadvantages have prompted a search for oral anticoagulants that are more predictable in their anticoagulant effects, easier to administer and potentially safer. Other oral vitamin K antagonists are being explored, as well as two alternate classes of anticoagulants: direct thrombin inhibitors (DTIs) and factor Xa inhibitors. They have minimal drug and food interactions and require no dosage adjustments or hematologic monitoring. DTIs include ximelagatran and dabigatran, the first new anticoagulant to receive FDA approval. The earliest member of this class is ximelagatran. It is proven non-inferior to dose-adjusted warfarin, with a similar rate of major bleeding with both treatments (2). Its hepatotoxicity causes its withdrawal prior to FDA review. Its value is proof of principle that a DTI could be at least as effective as warfarin in high-risk AF patients, without the logistic drawbacks of warfarin. Dabigatran does not require INR monitoring and can be considered more cost-effective than vitamin K antagonists for IS prevention of AF patients in Switzerland (34).

The RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy, Warfarin, Compared with Dabigatran) trial compares dabigatran with dose-adjusted warfarin in 18113 patients with NVAF concerning IS, hemorrhagic stroke and systemic embolism (12).

Two doses of dabigatran are compared with warfarin and although the dose of dabigatran is double-blinded, assignment to warfarin or dabigatran is not blinded. Low-dose dabigatran (110 mg BID) is non-inferior to warfarin for all stroke and systemic embolism (1,53% per year for dabigatran versus 1,69% per year for warfarin; $p<0,001$ for non-inferiority). High-dose dabigatran (150 mg BID) is superior to warfarin (1,11% versus 1,69% per year; $p<0,001$ for superiority). Most benefits of high-dose dabigatran over warfarin are for IS prevention, with a 36% relative risk (RR) reduction in favour of the former ($p<0,001$). Low-dose dabigatran demonstrates safety superior to that of warfarin, with significantly less major bleeding (2,71% versus 3.36% per year; $p=0,03$). The risk of major

intracranial and extracranial bleedings with high-dose dabigatran is insignificantly lower than that with warfarin (3,11% versus 3,36% per year; $p=0,31$). Although all anticoagulant-associated bleeding has the potential to be life-threatening, anticoagulation-associated hemorrhagic stroke carries a 76% risk of death or permanent disability and is the most feared complication of this therapy (20).

Based on the results of the RE-LY trial, dabigatran (Pradaxa, Boehringer-Ingelheim) is approved by the FDA in October 2010 for IS prevention in NVAF patients at a dose of 150 mg BID in patients with creatinine clearance >30 mL/min and 75 mg BID in those with creatinine clearance between 15 and 30 mL/min. Even among patients with moderate renal impairment, the 150-mg dose of dabigatran is more effective than the 110-mg one as it diminishes IS incidence rate by almost half (1,3 versus 2,4 events/100 patient-years) while not increasing major bleeding incidence rate (5,3 versus 5,7 events/100 patient-years) (7,49). The 110-mg dose is approved in most other countries, including those of Europe.

An analysis of RE-LY data concerning the bleeding risks associated with either dose of dabigatran indicates that extracranial bleeding rates increase with age and are comparable to or slightly higher than those with warfarin in patients aged over 75 years. Intracranial bleeding rates are significantly lower than those with warfarin and are not affected by age (RR for 150 mg dabigatran compared to warfarin: 0,43 in patients under the age of 75 years and 0,42 in patients aged 75 years or more) (18). Dabigatran is more cost-effective than warfarin for patients at a high ($\text{CHADS}_2 \geq 3$) moderate ($\text{CHADS}_2 \geq 2$) risk for IS provided that the time in the therapeutic range is greater than 57,1% (41). It is not cost-effective for patients with a $\text{CHADS}_2 = 1$, although another analysis (21) concludes otherwise, primarily due to methodological differences. Both analyses are conducted based on cost data in the USA and can't be applicable in other countries.

Tecarfarn is a new oral vitamin K epoxide reductase antagonist (19). It is a structural analogue of warfarin, highly protein bound (99%) and metabolized by carboxyl esterases in liver microsomes. Its mechanism of action is identical to

that of warfarin, although it differs substantially in that it is not metabolized by the CYP450 system. It offers the possibility of effective anticoagulation that can be monitored by INR, but with fewer CYP450-mediated drug-drug and drug-food interactions.

Two oral factor Xa inhibitors, rivaroxaban and apixaban, are investigated as alternatives to warfarin for IS prevention in high-risk AF patients. They present with potential advantages over warfarin similar to those of DTIs such as consistent dosing without significant food or drug interactions or the need for monitoring. The ROCKET-AF trial demonstrates that rivaroxaban is non-inferior to warfarin for the prevention of IS or systemic embolism. However, unlike dabigatran, rivaroxaban does not decrease the risk of IS. The overall risk of major and non-major clinically relevant bleeding is comparable, but there is a lower risk of intracranial and fatal bleeding in the rivaroxaban group (32).

Apixaban is compared to warfarin in the ARISTOTLE trial (Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation) involving 18201 patients with a mean CHADS_2 of 2,1 and a median follow-up duration of 18 years. Patients are randomized to a twice daily dose of apixaban (5 mg) or warfarin titrated to an INR of 2,0-3,0. Apixaban is superior to warfarin for the prevention of IS and systemic embolism (hazard ratio = 0,79; $p=0,01$) and presents with a lower risk of bleeding (hazard ratio = 0,69; $p<0,001$) (22).

Thrombolysis is administered for 31 out of 698 cases (5%) with first-ever and recurrent cerebral infarction in Japan. Its rate is 16% of 197 cerebral infarction patients admitted within three hours of onset (25).

OCCLUSION DEVICES

Autopsy studies suggest that most cerebral emboli in patients with AF originate in the LAA. It is theoretically desirable to isolate the LAA from the circulation, presumably preventing embolism from this site, even after anticoagulation is ceased. The non-randomized continued access protocol registry for the Watchman device shows a lower complication rate such as pericardial effusion and suggests that greater operator experience decreases the rate of major complications (36). LAA exclusion protects against AF-related IS and other embolic

complications through different strategies such as surgical amputation or ligation, percutaneous endocardial occlusion by deployment of occlusive devices, and ligation of the LAA via a closed-chest, percutaneous, epicardial catheter-based approach in selected patients (4).

A second type of LAA occlusion device, the Amplatzer Cardiac Plug (AGA, Minneapolis, MN, USA) is implanted in patients with contraindications to warfarin in Asia and Europe. Postimplantation treatment is 1-3 months of clopidogrel and lifelong aspirin. Initial results from 19 patients in the Asia study show no residual leakage around the device and no cases of IS or systemic embolism at a mean follow-up of 12,7 months (28).

Emergent stent-assisted endovascular carotid artery thrombolysis of IS due to acute cervical internal carotid artery occlusion results in excellent recanalization rates and favourable clinical outcomes as assessed by using NIHSS scores (15). Twenty patients undergo mechanical thrombectomy for large vessel occlusion by means of Merci (MER), Penumbra (PEN) or Solitaire-FR (SOL) procedures. Complete recanalization is achieved in 59,1% of the cases, i. e. in 40% - with MER, in 45,5% - with PEN, and in 100% - with SOL. The SOL device presents with a significantly higher rate of angiographic recanalization, requires a lesser number of passes and other associated than MER and PEN (1). SOL is used as the first-line device to restore blood flow in 141 acute IS patients at a mean age of 66 years and median NIHSS score of 18. Of them, 74 patients have received intravenous tissue-type plasminogen activator before endovascular treatment. There is complete revascularization in 120 of 142 occlusion sites (85%) and good outcome in 77 of 141 patients (55%). The latter is more frequent in patients on this drug therapy (in 66% versus 42%; $p < 0,01$) (16).

PREVENTION

A meta-analysis of eight cohort studies from the United States, Northern Europe, Australia, and Japan published between January 1990 and May 2012 reveal that total dietary fiber intake is inversely associated with risk of first hemorrhagic stroke plus IS. However, soluble fiber intake (4 g/day) does not relate to IS risk reduction. Recent findings support

dietary recommendations to increase intake of total dietary fiber (46).

Alternative IS prevention strategies could spare patients with infrequent or short-lived paroxysms of AF the risks and inconveniences of continuous anticoagulation. These strategies are examined in individuals with dual-chamber pacemakers, cardioverter-defibrillator and cardiac resynchronization therapy defibrillator devices. Current device technology allows for nearly real-time continuous remote monitoring and thus patients with infrequent AF episodes may start and stop anticoagulation only around the time of an AF episode.

A final strategy to prevent IS and to reduce the risk of this pathology in AF patients is to maintain them in sinus rhythm ('rhythm control'). AF is asymptomatic, symptoms are unreliable measures of rhythm control in those patients who do have them, antiarrhythmic drugs are often unsuccessful at maintaining sinus rhythm. Symptomatic AF episodes can be converted into asymptomatic ones by drug or ablation therapy. There is rising interest in the possibility that newer approaches to AF treatment may provide sufficient rhythm control to allow the cessation of anticoagulation. Novel antiarrhythmic agents are associated with a reduced risk of IS (11). In the 'A Trial with Dronedarone to Prevent Hospitalization or Death in Patients with Atrial Fibrillation' study, dronedarone diminishes the risk of IS in AF patients. Potential mechanisms for this reduction include decreasing blood pressure and lowering heart rate. Although it is possible that the reduced IS incidence rate is due to the patients having better rhythm control, even patients who are commonly with AF exhibit this decreased rate (11).

Patients with high-risk AF who can tolerate anticoagulation have three options for IS prevention. Warfarin, dabigatran and rivaroxaban each have individual risks and lifestyle benefits that must be considered with each patient. In some patients unable or unwilling to use anticoagulants indefinitely, the risk-benefit ratio may favour the combination of aspirin and clopidogrel, or percutaneous LAA occlusion, for better IS prevention than aspirin monotherapy. New cardiac monitoring technology offers clinicians the ability to detect AF and the usage

of selective anticoagulation. Such advances improve the outlook for preventing both first and recurrent IS in patients at risk for AF-related cerebrovascular disease.

Promising neuroprotection that meets the Stroke Academic Industry Roundtable criteria and is based on a more profound understanding of the complex IS pathophysiology such as inhibitors of NADPH oxidases and PSD-95, hypothermia and ebselen, a seleno-organic compound with glutathione peroxidase-like activity, is nowadays intensively evaluated (30).

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