Prevention Strategies for Cardioembolic Stroke: Present and Future Perspectives

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Abstract: Atrial fibrillation (AF) is the most common cause of cardioembolism. An update on secondary prevention strategies, used to protect patients from the risk of stroke in many common cardiac conditions, is presented in the paper. The main line of actions of stroke prevention in cardioembolism is mostly connected with antithrombotic drugs, but also other, more invasive, techniques are quickly emerging. Also the classic pharmacological prevention with coumarins may soon be overcome by new generation anticoagulants. Is an aggressive treatment of Patent Foramen Ovale (PFO) always recommended? One of the main challenges of the future years will be to understand competitiveness between old and new preventive strategies.

Keywords: Cardioembolic stroke, risk factors, secondary prevention, antithrombotic drugs, atrial fibrillation, PFO.

INTRODUCTION

Cardioembolism accounts for about 20% of all ischemic strokes. Cardioembolic strokes are usually severe, prone to early recurrence and to hemorrhagic transformation. Also long -term recurrence and mortality are higher, probably due to the underlying pathogenetic mechanism. Clinical features may help to suspect a cardioembolic source, but usually have low sensitivity: these could be, sudden onset to maximal deficit, quick regression of symptoms, simultaneous or sequential strokes in different arterial territories, hemorrhagic transformation of an ischemic infarct, early recanalization of an occluded vessel. The confirmation of the cardiac origin or its discovery is based on cardiac functional and imaging techniques such as electrocardiogram, Holter monitoring, echocardiography. Various cardiac conditions have been clearly associated with an increase in the risk of ischemic stroke (Table **1**). Because certain stroke risk factors, like hypertension, may also be determinants of cardiac disease, some cardiac conditions may be viewed as intervening events in the causal chain for stroke. Cardiac factors that independently increase the risk of stroke include AF, valvular heart disease, myocardial infarction, coronary artery disease, congestive heart failure [1, 2]. Improved cardiac imaging has led to increased detection of potential predisposing conditions, such as patent foramen ovale (PFO), atrial septal aneurysms, aortic arch atherosclerotic disease, mitral anular calcification, spontaneous left atrial appendage echo contrast and valvular strands (thin filamentous material). Considerable advancements in relation to some cardioembolic conditions have occurred in recent years, especially in atrial fibrillation (AF), several evidence-based treatment strategies have emerged and novel therapeutic options will be available for the future. For other cardioembolic disorders there are still partial knowledge and conflicting opinions that limit the establishment of defined guidelines. This chapter provides an overview of the current state of knowledge for the major cardioembolic stroke risk factors and the strategies of primary and secondary prevention with particular interest to future therapeutical perspectives.

Table 1. Cardiac Risk Factors for Ischemic Stroke

DEFINITE	POSSIBLE/PROBABLE
Atrial	**Atrial**
Atrial Fibrillation	Patent foramen ovale
Substained atrial flutter	Atrial septal aneurysm
Sick sinus syndrome	Atrial or ventricular septal defects
Atrial mixoma	
Left atrial appendage thrombus	Spontaneous echocontrast in left atrial appendage
Ventricular	**Ventricular**
Acute myocardial infarction	Subaortic hypertrophic cardiomiopathy
Left ventricular failure	
Left ventricular thrombus	**Cardiac valves**
Dilated myocardiopathy	Mitral valve prolapse
Cardiac valves	Calcified aortic stenosis
Mitral stenosis/calcifications	Valve strands
Prosthetic valves	Fibroelastoma

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ATRIAL FIBRILLATION (AF)

Atrial Fibrillation is the most important cause of cardioembolic stroke. In Western countries AF is mainly associated with hypertensive and ischemic heart disease, but it can also occur in absence of any cardiac pathology (lone AF), while rheumatic mitral valve disease seems to be now very rare in industrialized areas. For this reason the following paragraphs relates only to non-valvular AF. The overall prevalence is approximately 1%, but the prevalence among those older than 65 years is close to 6%. Therefore, the attributable risk of stroke due to AF increases significantly with age, approaching the risk of hypertension among patients 80 to 89 years old. Approximately, 16% (11% to 29%) of all ischemic strokes are associated with AF [3], and among patients over 70 years old with ischemic stroke, more than one-third suffer from AF [1]. AF increases the relative risk of ischemic stroke about five-fold, roughly 1% to 5% per year for elderly people [3]. Loss of atrial contraction in AF leads to blood stasis, particularly, in the left atrial appendage which is a known pro-thrombotic condition.

Standards in Cardioembolism Prevention

Prevention of systemic embolism is achieved by means of restoration and control of sinus rhythm or with permanent anti-thrombotic treatment. Concerning the selection of the most appropriate antithrombotic regimen, clinical trials demonstrated that anticoagulation is more effective than aspirin. Five trials of primary prevention (AFASAK, SPAF I, BAATAF, CAFA, SPINAF) comparing warfarin vs. placebo found a relative risk reduction of 2.5% to 4.7% per year for ischemic stroke and absolute stroke rate reduction of 33% to 86% [3]: a recent meta-analysis of anti-thrombotic therapies for primary and secondary prevention of stroke in AF by Hart and collegues [4] confirmed the relative reduction in stroke risk with warfarin compared to placebo (64%; 95%CI 49% to 74%). The meta-analysis also showed a lower reduction in the relative risk of stroke when using antiplatelet therapy (8 trials, 4876 participants): 22% (95%CI 6% to 35%) [4]. Comparing directly warfarin with anti-platelet drugs, alone or in combination (e.g. aspirin plus clopidogrel in the ACTIVE W trial), the anticoagulation therapy reduced the relative risk of stroke of 39% (95%CI 22% to 52%; 12 trials, 12963 patients) [4]. Therefore the meta-analysis by Hart and colleagues validates that warfarin is more efficacious than aspirin in stroke risk reduction in primary and secondary prevention studies. The combination of warfarin plus antiplatelet drugs was tested versus warfarin alone in a meta-analysis of ten randomized trials by Dentali and collegues [5], but it didn't show an additive beneficial effect, while the risk of bleeding was increased in patients receiving the combination therapy (1.43; 95%CI 1.00 to 1.25). Only the study NASPEAF [6] (National Study for Primary Prevention of Embolism in Non-rheumatic Atrial Fibrillation) reported a reduction in vascular events in the group of the combination of triflusal and acenocoumarol compared with warfarin alone (hazard ratio 0.33; 95%CI 0.12-0.91).

The beneficial effect of warfarin in stroke risk prevention must be balanced with the risk of hemorrhage complications. The absolute risk of hemorrhage in patients with AF on warfarin calculated from randomized clinical trials averaged 2% per year, one quarter of which (0.3% to 0.6%) were intracranial haemorrhage [7, 8]. The risk of intra-cranial hemorrhage was doubled with warfarin compared with aspirin, although the increase in absolute risk was small (0.2% per year). In the BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged study) [9], a randomized clinical trial of warfarin versus aspirin in the elderly (age>75 years), the risk of hemorrhage was similar in both treatment groups, raising concern of possible selection bias like restriction to patients with moderate risk of stroke.

Risk Stratification for Patients with AF

Assessment of thromboembolic risk in AF is essential to guide the use of anticoagulation or anti-platelet therapy. In a recent systematic review of risk factors for stroke in AF patients, four clinical features emerged as consistent predictors: prior TIA or stroke (RR 2.5, 95%CI 1.8 to 3.5), increasing age (RR 1.5 per decade, 95%CI 1.3 to 1.7), history of hypertension (RR 2.0, 95%CI 1.6 to 2.5) and diabetes mellitus (RR 1.7, 95%CI 1.4 to 2.0) [10]. Several risk factors stratification schemes (CHADS2, SPAF, AFI1, Framingham, ACCP, ACC/AHA/ESC guidelines, NICE/Birmingham) [11] have already been published, but evident differences exist between them. The most popular and validated of these schemes is the CHADS2 [11] (see Table **2**) which relies on the previous four clinical predictors plus congestive heart failure, making its use simple for everyday clinical practice. Other variables that could ameliorate the risk stratification have been investigated, but conflicting results have been reported. Among these, echocardiographic findings: a pooled analysis of three studies, BAATAF, SPINAF, and SPAF I, showed that moderate to severe left ventricular dysfunction, but not left atrial size, was an independent predictor of stroke [12]; Shively and collegues [13] noted increased stroke risk associated with decreased left atrial flow velocity (<15 cm/sec), ventricular dilatation, and decreased left atrial ejection fraction in patients with AF and atrial enlargement; In another study, spontaneous echo contrast was significantly associated with AF-related stroke [14]. Coronary artery disease and female gender are also less certain risk modifiers,

Table 2. CHADS2 Scheme

RISK FACTORS	POINTS	TOTAL SCORE	RISK OF STROKE
Prior stroke or TIA	2	3-6	High 5.9% - 18.2% per year
Age > 75 years	1		
Diabetes mellitus	1	1-2	Intermediate 2.8% – 4% per year
Arterial hypertension	1		
Congestive heart failure	1	0	Low 1.2% -3% per year

but the latter was included as risk factor in two stratification schemes (SPAF and Framingham) [11].

The decision to use anticoagulant or aspirin depends on risk stratification of patients with AF. Aspirin carries a lower bleeding risk and requires less medical monitoring than do anticoagulants, but has a lower stroke risk reduction effect. Recent published guidelines for the management of atrial fibrillation [15], in particular for stroke prevention, recommend the use of anticoagulation in patients with more than 1 moderate risk factors (age 75 years or older, hypertension, heart failure, ejection fraction below 35% or fractional shortening less than 25% and diabetes mellitus) (level of evidence A). Aspirin, 81–325 mg daily, is recommended as an alternative to vitamin K antagonists in low-risk patients or in those with contraindications to oral anticoagulation (level of evidence A). For patients with less validated risk factors or with only 1 risk factor it is reasonable to choose the antithrombotic therapy based upon an assessment of the risk of bleeding complications, ability to safely sustain adjusted chronic anticoagulation, and patient preferences (level of evidence A). The same criteria in selecting the antithrombotic therapy should be used irrespective of the pattern (i.e., paroxysmal, persistent, or permanent) of AF (level of evidence B).

When to Start with Anticoagulation?

The issue of when to initiate anticoagulation treatment in a patient with AF with stroke or TIA is extremely important on the light of the high risk of stroke recurrence in the first two weeks and of the high risk of haemorrhagic transformation of the cerebral infarct (Fig. **1**). The recent meta-analysis by Paciaroni and collegues [16] and the update by Guedes and Ferro [17], addresses this issue evaluating 8 randomized trials comparing anticoagulants (unfractionated heparin or low-molecular-weight heparin or heparinoids) started in the first 48 hours with other treatments in patients with acute ischemic cardioembolic stroke. The results of the meta-analysis didn't show a significant reduction in recurrent ischemic stroke within 7 to 14 days with anticoagulation compared with other treatments (3.0% *versus* 4.9%. OR 0.68, 95% CI 0.44 to 1.06, p=0.09), while the symptomatic intracranial bleeding were increased with early anticoagulation therapy (2.5% *versus* 0.7%, OR 2.89, 95% CI 1.19 to 7.01, p=0.02). Death or disability at final follow up were similar in the two groups (73.5% *versus* 73.8%, OR 1.01, 95%IC 0.82 to 1.24, p=0.9). The difference in death and disability was statistically significant in only one trial (58.5% *versus* 74.1%, OR 0.49, 95%IC 0.26 to 0.93) [18] which was the only study with anticoagulation therapy started within 3 hours from stroke onset. The positive effect of early heparin could be ascribed, as suggested by several studies [19, 20], also to its anti-inflammatory properties than to its antithrombotic ones. However additional clinical trials in the three-hour period are needed to confirm this finding. Current guidelines and usual practice recommend that anticoagulation should be started as soon as possible in patients with AF after brain imaging for a TIA and should be delayed in ischemic stroke, according to ischemic lesion extension, clinical severity and cardiologic comorbidity, stroke in favour of anti-platelet therapy [1, 21].

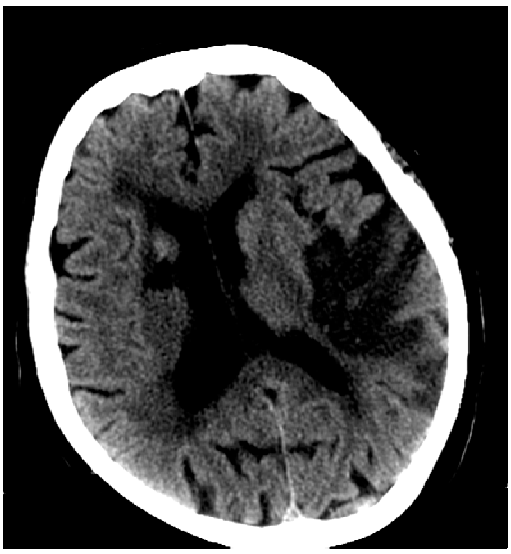

Fig. (1). Cardioembolic stroke: left hemispheric middle cerebral artery infarction with visible bleedings (petecchiae) and sulci effacement.

Future Treatment Perspectives in AF

Future strategies for stroke prevention in AF include i) fixed low-dose warfarin anticoagulation; ii) new oral anticoagulant drugs; iii) non-pharmacological approaches.

One meta-analysis reported that fixed low-dose warfarin compared with adjusted-dose warfarin was associated with more thromboembolic events without reducing the risk of bleeding complications [22]. New oral anticoagulant drugs are currently in development owing to the many limitations of vitamin K antagonists. There are two main types of these agents: direct thrombin inhibitors (DTIs) and oral factor Xa inhibitors (FXaI). The first DTI tested was ximelagatran, that showed in a phase III clinical trial a significant reduction in terms of prevention of stroke in AF compared to warfarin, but was then abandoned because of hepatotoxicity in a substantial number of patients [11]. Others DTIs like dabigatran and megalatran are currently under investigation. Dabigatran has been recently investigated in the RE-LY trial [23], which randomly assigned 18,113 patients who had atrial fibrillation to receive fixed doses of dabigatran (110 mg or 150 mg twice daily) or adjusted-dose warfarin: the risk of stroke was reduced in patients receiving dabigatran at a dose of 150 mg twice daily respect to warfarin (95% CI 0.53 -0.82, p<0.001 for superiority) and the risk of major bleedings was reduced in patients receiving 110 mg of dabigatran twice daily respect to warfarin (p=0.003); the study also demonstrated the non-inferiority of the 110 mg dose of dabigatran versus warfarin in stroke reduction and of the 150 mg dose of dabigatran versus warfarin in major bleeding risk. The major advantage of dabigatran respect to warfarin is that it doesn't need dose adjustment and therefore it should be less prone to inadequate anticoagulation. The parenteral FXaI idraparinux has been compared to warfarin in the AMADEUS trial in patient with AF, but clinically bleeding complications were significantly higher in the idraparinux group (19.7% *vs* 11.3%, p=0.007) and the drug achieved the criteria of non-inferiority [24]. Other oral FXaI like rivaroxaban and apixaban are currently under investigation. Furthermore a new

orally active, selective, reversible FXa inhibitor, DU-176b [N-(5-Chloropyridin-2-yl)-N-[(1S,2R,4S)-4-(N,Ndimethylcarbamoyl)-2-(5-methyl-4,5,6,7-tetrahydrothiazolo [5,4-c]pyridine-2carboxamido)cyclohexyl]ethanediamide p-toluenesulfonate monohydrate], is currently under investigation. In non-clinical studies [25, 26], DU-176b showed excellent potential as an antithrombotic agent. Non-clinical data indicate no evidence of liver function abnormalities in study animals exposed to DU-176b. In Japan, two early phase 2a, DU-176b, open-label, dose-escalation studies were conducted in a total of 56 subjects with nonvalvular AF. Subjects were treated for 6 to 10 weeks with total daily doses of 5 mg to 120 mg: the doses evaluated in this study were well tolerated, no major bleeding was reported. There was one clinically relevant non-major bleeding reported for each of the following DU-176b regimens: 30 mg bid, 45 mg bid, and 60 mg bid [26]. There were no others observed clinically relevant liver function abnormalities. A phase 3, randomized, double-blind, double-dummy, parallel-group, multi-center, multi-national study for evaluation of efficacy and safety of DU-176b versus warfarin in subjects with atrial fibrillation, ENGAGE AF-TIMI48 trial (Effective Anticoagulation with factor xA next Generation in Atrial Fibrillation) is currently ongoing: data from this study are expected for 2011.

The non-pharmacological approaches for stroke prevention can be divided in an electrophysiological approach like ablation techniques with the aim of restoring the sinus rhythm and a mechanical approach with the aim of preventing the formation of thrombus in left atrium appendage or to divert it from the cerebral circulation.

The electrophysiological approach is based on two types of ablation procedures, the "maze" procedure that involves complex lesioning of the left atrium and the pulmonary veins isolation [27]. In selected series the pulmonary veins isolation appears to prevent symptomatic AF in 80% to 90% at 1 year of follow-up [1, 27], but there are no data about the durability of this effect.

The rationale behind the mechanical approach is that the most of thrombi that then embolise originates from the left atrium appendage where there is an hypercoagulable state because of the blood stasis. Today, surgical excision of the left atrium appendage is routinely performed as an adjunct to cardiac surgery in those cases at high risk for left atrium appendage-related thromboembolism. The North American guidelines for management of patients with valvular heart disease recommend amputation of the left atrium appendage at the time of mitral valve surgery to reduce the risk of stroke [28]. Exclusion of the left atrium appendage can also be performed thoracoscopically under general anesthesia by applying a loop snare or by stapling the base of the left atrium appendage. Occlusion, as opposed to ligation or amputation, of the left atrium appendage can also be performed using three percutaneous-catheter-based systems: the Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO®) system, the WATCHMAN® system and the AMPLATZER® [28]. The development of left atrium appendage occlusion systems provides a promising alternative to anticoagulation, specially for patients at high risk of AF-related stroke who cannot tolerate anticoagulation. However safety and effectiveness must be still verified by additional studies. In initial studies, complications requiring surgical exploration (e.g. device embolisation, pericardial tamponade, stroke, and death) occurred at higher than acceptable frequencies [28].

PATENT FORAMEN OVALE (PFO)

During the last decade, there has been an increasing emphasis on the role of patent foramen ovale (PFO) in the genesis of ischemic juvenile stroke. Several case control studies and a meta-analysis [29,30] have shown that PFO was significantly associated with stroke in patients younger than 60 years of age, in particular in the subgroup of young patients with cryptogenic stroke. A recent case-control study by Handke and collegues [31] has shown that also in the age group of patients older than 55 years with cryptogenic stroke the prevalence of PFO was significantly greater than in patients with non-cryptogenic stroke with an odds ratio after the multivariate analysis of 3.00 (95%CI, 1.73 to 5.23; $p<0.001$) [31]. The previous meta-analysis by Overell and collegues [29] didn't show a significant risk associated with PFO in patient older than 55 years with cryptogenic stroke based on three studies (only one of these studies had shown a significant risk in patients older than 55 years) [32]. In the study by Homma and collegues [33] in an exploratory analysis of patients with cryptogenic stroke from the PICSS study (PFO in Cryptogenic Stroke Study), the PFO significantly increased the risk of adverse events at two years of follow-up in patients older than 65 years but not in patients younger than 55 years ($p=0.01$; hazard ratio 3.21; 95% CI, 1.33 to 7.75). The controversial findings of these studies have raised concern in commentaries about the selection of the study populations and further studies are needed to investigate the issue. Cerebral paradoxical embolism is usually a presumed diagnosis, because direct evidence, such as a thrombus lodged in the PFO shown on transesophageal echocardiography or the discovery of a deep venous thrombosis, is commonly lacking. Despite these ongoing controversies, it is reasonable to incriminate a cerebral paradoxical embolism in young patients with no other identified cause of stroke than PFO.

The optimal treatment of these patients remains a matter debate, mainly because of a lack of controlled clinical trials. There are four therapeutic options: antiplatelets drugs, anticoagulants, closure of PFO by transcatheterization or closure of PFO by surgery. The only two studies [34,35] of secondary prevention of stroke in patients with PFO show that the risk of recurrent stroke is relatively low, about 1% per year, in patients treated with aspirin or short-term anticoagulation. In the Lausanne Study [34] and the French Study Group [35], the annual rate of TIA was 3.8% and 3.4%, of stroke alone, 1.9% 1.2%, respectively.

At present, there is little information on the risk of stroke recurrence in those with PFO associated with an atrial septal aneurysm (ASA) compared to PFO alone, and some have suggested that PFO with an ASA, or large PFOs with right-to-left shunting, have more stroke risk [36, 37]. Several factors have been suggested to increase the risk for stroke or recurrent stroke in patients with PFO: these includes a younger age [29], the association with atrial septal aneurysm (ASA) [29, 38], the presence of a right-to-left shunt at rest, the size of the PFO [39, 40], the association with thrombophilic conditions [41]. Despite a meta-analysis and other studies have reported a strong increase in stroke risk and stroke recurrence in patients with both PFO and ASA com-

pared with PFO alone, specially in cryptogenic stroke, other studies failed to confirm this association [32, 33]. Also for the other presumed risk factors further evaluations are needed because of controversial findings. On these grounds, Nendaz *et al*. [42] created a decision analysis model for the clinician. This model indicates that for a stroke risk recurrence of 1.4% to 7% per year, there was more benefit from surgical closure of the PFO than from any other treatment. When the risk is from 0.8% to 1.4% per year, anticoagulants and antiplatelets are better than placebo, while when it is <0.8% per year, neither medical nor surgical treatment is indicated. Further studies are planned to determine the stroke risk in subgroups of PFO patients using transcranial Doppler ultrasound with the microbubble technique, which may be more accurate than transesophageal echocardiography [43]. At present, treatment is limited to the application of empirical clinical criteria. Useful clarifications for the best approach in the long- term management of PFO with TIA or stroke could come from the epidemiological data of the Forame Ovale Registro Italiano (FORI), a multicentric registry based in Perugia, established in 2003.

Surgical closure of PFO without stroke recurrence has been reported [44, 45], but others have not been so fortunate [46]. A minimally invasive alternative to surgery consists in transcatheter closure of the PFO. The procedure involves the percutaneous implantation of a device to occlude the interatrial septum (CardioSEAL® and Amplatzer®, approved by FDA). The reported complications following PFO closure are infrequent and are associated with low morbidity and mortality. Adverse events includes brief atrial fibrillation (0.8%), device dislodgement (0.4%), device arm fracture (3.6%) and surgical explanation (0.8%) [47]. However long-term consequences of PFO closure are unknown. A review of 12 uncontrolled case series of more than 100 patients documented a rate of stroke recurrence during the first year after transcatheter PFO closure between 0 and 5% [46]; the percentages during the other years of follow-up varied considerably between the different studies. Current data suggest that transcatheter closure is at least effective as medical treatment, but further studies are necessary to investigate this issue.

The use of coumarins is risky in young patients with a long life expectancy because of the major bleeding risk, estimated at 1.5% to 11% per year [45]. The ACCP guidelines [48] recommend anti-platelet therapy in patients with ischemic stroke and PFO; anticoagulants are recommended when a deep venous thrombosis (DVT) is demonstrated by ultrasound investigation or by venography, when there is association with an underlying hypercoagulable state and before closing the PFO in those with a presumed higher risk of stroke recurrence. PFO closure might be considered for patients with recurrent cryptogenic ischemic strokes, despite antithrombotic therapy or after the first event in patients with high-risk conditions such as presence of DVT, hypercoagulable state, characteristic of PFO documented by transesophageal echocardiography. In practice, and until results of future studies focusing on risk stratification are reported, the following criteria could be applied to decide secondary prevention therapy in patients with stroke and PFO (Table **3**): (1) more than one cerebrovascular event clinically or on MRI scan, (2) evidence of DVT, (3) demonstration of an hypercoagulable state, (4) significant right-to-left shunting through the PFO documented by echocardiography or Doppler, (5) PFO associated with ASA and (6) a history of Valsalva's manoeuvre just before the clinical event.

PROSTHETIC HEART VALVES (PHV)

In the last decades the replacement of heart valves constantly increased: considering only aortic valve disease, more than 200,000 replacements are currently performed annually worldwide [49].

In patients with prosthetic heart valves, thromboembolic events occur at a rate of 7 to 34% per year without anticoagulant therapy and at a rate of 1 to 5% per year with oral anticoagulation [50]. Two types of PHV are used: bioprosthetic valves and mechanical valves. Both mechanical and bioprosthetic valves are at increased risk of stroke, which however is confined in the latter to the first months after implantation, while it is long-lasting in the former; the last decade have seen a dramatic reduction in the use of mechanical valves (aortic valve: 21% mechanical vs. 79% of

Table 3. Secondary Prevention in Patients with PFO-Associated Stroke: Risk Stratification-Based Recommendations

RISK STRATIFICATION	HIGH RISK	MODERATE RISK	LOW RISK
Absolute criterion			
No other potential cause of stroke than PFO	Required	Required	Required
Major criteria			
Evidence of deep vein thrombosis	1 criterion	1 criterion	0 criterion
Evidence of a hypercoagulable state			
Stroke recurrence despite antithrombotic treatment			
Minor criteria			
Massive right-to-left shunt	≥1 criteria	0 criteria	0 criterion
Interatrial septal aneurysm			
Multiple clinical cerebrovascular events and/or multiple ischemic lesions at brain MRI			
Recommended therapy:	Transcatheter closure	Anticoagulation INR 2-3 / closure	Anti-platelet therapy

bioprosthetic [49]; mitral valve: 55% repair techniques, 28% mechanical, 17% bioprosthetic [51]) mostly because of the need of a life-long anticoagulant therapy. Thromboembolic risk associated with PHV is also related to the site of valve replacement, being higher for mitral valve than for aortic valve, and to the kind of mechanical valve used, being lower for the bileaflet ones than for monoleaflet and caged ball ones. The presence of other risk factors, such as AF, left ventricular dysfunction, spontaneous echocardiographic contrast in the left atrium and increasing age obviously also increase the chance of embolism [52]. Stroke may occur from either inadequate anticoagulation or because thrombogenic factors are inadequately suppressed despite adequate anticoagulation therapy. The precise pathophysiology of thromboembolism in patients with PHV remains uncertain. Increased shear rates at the valve surfaces may activate platelets, generating platelet-derived microparticles, which could have potent procoagulant activity. Furthermore, the presence of microemboli, frequently encountered in these patients, may result from harmless gaseous bubbles (cavitation) [53].

As yet, no prospective randomized studies have been done in patients with mechanical valves to assess the efficacy of antithrombotic therapy. In a meta-analysis comprising more than 53,000 patient-years, the major embolism rate without antithrombotic therapy was 4.0% per year, reduced to 2.2% year with antiplatelets and to 1.0% per year with anticoagulants [50]. Current guidelines of the ACCP [48] recommend the use of anticoagulation with an INR range of 2 to 3 for bileaflet mechanical aortic valves, with an INR range of 2,5 to 3,5 for mechanical mitral valves and for monoleaflet valves; in case of stroke during anticoagulation or if there are concomitant vascular risk factors, it is recommended the use of anti-platelet therapy like aspirin 75-100mg per day in addition to anticoagulation (INR range 2,5 to 3,5); in patients with bioprosthetic valves it is recommended anticoagulant therapy for the first 3 months after implantation followed by anti-platelet therapy.

ACUTE MYOCARDIAL INFARCTION (AMI)

About 1% to 5% of patients with AMI have an ischemic stroke, most of them cardioembolic, occurring within two to four weeks. Stroke occurred especially in those with anterior AMI, in whom the risk of ischemic stroke raises to 12% [3], and in patients with large anterior infarcts [54]. In the first month after AMI, incidence rates were 1% to 3.2%, and AF and ST segment elevation were significant predictors [55]. Left ventricular thrombi, in older patients with large transmural infarcts, especially those with congestive heart failure, have an increased risk of stroke. Transesophageal echocardiography is needed to diagnose ventricular thrombosis, but it should be performed at least 24 hours after AMI, because these develop usually 1 to 10 days after AMI. Approximately 15% of AMI patients with recognized LVT will suffer stroke [3]. No randomized trials have been carried out comparing aspirin to anticoagulants to prevent stroke following AMI, though anticoagulants alone were shown effective in preventing recurrent AMI (INR 2.8 to 4.8) and stroke in the Anticoagulants in Secondary Prevention of Events Coronary Thrombosis (ASPECT) trial. No comparison with aspirin was ever made [56]. Early randomized trials showed that heparin followed by low-intensity oral anticoagulation (INR 1.6 to 2.5) reduced stroke by about 70% in the weeks following AMI [3]. Being stroke rate three months after AMI so low, long-term anticoagulation beyond three months is not justified unless other major cardiac embolic risk factors, such as mural thrombosis, are present.

OTHER CARDIAC ARRHYTMIAS

Data concerning Atrial Flutter and Atrial Fibrillation-Flutter are scarce, and the exact risk of stroke associated with these conditions is unknown. Nevertheless, in a recent small study in patients without history of brain ischemia, the annual risk of stroke was only 1.6% [57]. In a recent prospective study of sick sinus syndrome (SSS), previous cerebral ischemic events, an age >65 years, left atrial spontaneous echocardiographic contrast and depressed atrial ejection force were independent risk factors for stroke [59,60]. Those with AF showed a thromboembolic rate of 5% per year, compared to 3.5% per year in those without AF [3], though a more recent study reported stroke rate of 10% per year [58,59]. Dual-chamber cardiac pacemakers reduced both the occurrence of AF as well as thromboembolism in comparison to ventricular pacing. For secondary prevention in patients with well established SSS, anticoagulation should be considered, irrespective of the presence or absence AF [3]. The value of antiplatelets, the optimal intensity anticoagulation, and the safety chronic anticoagulation in elderly patients still remains uncertain.

CONCLUSIONS

During the last decades many efforts have been focused on AF, by far the commonest cause of cardioembolic stroke, to establish evidence-based recommendations for primary and secondary stroke prevention: the use of long-term anticoagulation (INR 2–3) substantially reduced stroke recurrence risk and is now clearly established as a powerful treatment strategy; furthermore individualized treatment decisions based on risk factor stratification schemes like CHADS2, are now widely accepted and available to simply guide the clinician in the optimal anti-thrombotic strategy. On the other hand, however, there is still partial knowledge and conflicting results for other cardiac disorders like PFO, for which, although the real pathogenetic weight is still unknown, several aggressive treatment strategies, like implantation of cardiac devices for life-time, are quickly spreading in current clinical practice. Can the risk of unpredictable potential long-term complications be balanced by the treatment of a still partial known pathogenetic factor? Novel large, controlled clinical trials and the creation of large, diseases registries are expected to answer to these important questions. But above all, the hope for the next decade is directed to the development of new generation anticoagulants which could revolutionize the cardioembolic prophylaxis.

ABBREVIATIONS

AF	=	Atrial fibrillation
PFO	=	Patent foramen ovale
MRI	=	magnetic resonance imaging
DTIs	=	direct thrombin inhibitors
FXaI	=	factor Xa inhibitors
ASA	=	atrial septal aneurysm

DVT = deep venous thrombosis

PHV = prosthetic heart valves

INR = International Normalized Ratio

AMI = Acute myocardial infarction

SSS = sick sinus syndrome

ACCP = American College of Chest Physicians

ACC/AHA/ESC = American College of Cardiology/American Heart Association/ European Society of Cardiology

AFASAK = Atrial Fibrillation, Aspirin, and Anticoagulant Therapy Study

SPAF I = The Stroke Prevention in Atrial Fibrillation Study

BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation

CAFA = Canadian Atrial Fibrillation Anticoagulation

SPINAF = Silent Cerebral Infarction in Patients With Nonrheumatic Atrial Fibrillation

ACTIVE W = Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events

NASPEAF = National Study for Primary Prevention of Embolism in Non-rheumatic Atrial Fibrillation

BAFTA = Birmingham Atrial Fibrillation Treatment of the Aged study

CHADS2 = Congestive heart failure, Hypertension, Age, Diabetes mellitus, Stroke

RE-LY = Randomized Evaluation of Long-term anticoagulation therapY

ENGAGE = Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation

FORI = Forame Ovale Registro Italiano

ASPECT = Anticoagulants in Secondary Prevention of Events Coronary Thrombosis

PLAATO®. system = Percutaneous Left Atrial Appendage Transcatheter Occlusion

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