

Review Article

Antithrombotic Medication for Cardioembolic Stroke Prevention

M. Àngels Font,^{1,2} Jerzy Krupinski,³ and Adrià Arboix⁴

¹ *Institut d'Investigacions Biomèdiques de Bellvitge (IDIBELL), Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, 08907 Barcelona, Spain*

² *Department of Neurology, Hospital Sant Joan de Déu de Manresa (Fundació Althaia), Catalonia, 08243 Manresa, Spain*

³ *Department of Neurology, Cerebrovascular Diseases Unit, Hospital Universitari Mútua de Terrassa, Catalonia, 08227 Terrassa, Spain*

⁴ *Cerebrovascular Division, Department of Neurology, Hospital Universitari Sagrat Cor, University of Barcelona, C/Viladomat 288, Catalonia, 08029 Barcelona, Spain*

Correspondence should be addressed to Adrià Arboix, aarboix@hscor.com

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Embolicism of cardiac origin accounts for about 20% of ischemic strokes. Nonvalvular atrial fibrillation is the most frequent cause of cardioembolic stroke. Approximately 1% of population is affected by atrial fibrillation, and its prevalence is growing with ageing in the modern world. Strokes due to cardioembolism are in general severe and prone to early recurrence and have a higher long-term risk of recurrence and mortality. Despite its enormous preventive potential, continuous oral anticoagulation is prescribed for less than half of patients with atrial fibrillation who have risk factors for cardioembolism and no contraindications for anticoagulation. Available evidence does not support routine immediate anticoagulation of acute cardioembolic stroke. Anticoagulation therapy's associated risk of hemorrhage and monitoring requirements have encouraged the investigation of alternative therapies for individuals with atrial fibrillation. New anticoagulants being tested for prevention of stroke are low-molecular-weight heparins (LMWH), unfractionated heparin, factor Xa inhibitors, or direct thrombin inhibitors like dabigatran etexilate and rivaroxaban. The later exhibit stable pharmacokinetics obviating the need for coagulation monitoring or dose titration, and they lack clinically significant food or drug interaction. Moreover, they offer another potential that includes fixed dosing, oral administration, and rapid onset of action. There are several concerns regarding potential harm, including an increased risk for hepatotoxicity, clinically significant bleeding, and acute coronary events. Therefore, additional trials and postmarketing surveillance will be needed.

1. Introduction

Embolicism of cardiac origin accounts for about 20% of ischemic strokes. Several heart conditions enhance stroke risk. Atrial fibrillation is the most common condition of cardioembolic stroke, and anticoagulation is the treatment generally indicated for secondary prevention and in some cases for primary prevention. In this review, we analyse cardiac conditions prone to cardioembolic infarct and its management. We review atrial fibrillation, acute myocardial infarct, congestive heart failure and dilated cardiomyopathies, cardiac procedures, pacemakers, valve diseases, and endocarditis. We provide a table with AHA recommendations for patients with cardioembolic stroke types (Table 1) [1]. Transesophageal echocardiography has

also provided evidence that the aortic arch is a common source of embolic material, but the risk of cerebral embolism appears to be directly related to the size of atherosclerotic plaques visualized [2], so we have considered stroke due to atherosclerosis in this entity. Most common localization for cardioembolic stroke are total or partial areas supplied by major arteries of anterior and posterior circulation, most being cortical infarcts. Emboligenous cardiopathy, as the only demonstrable etiology has been found in only 4% of lacunar infarctions [3], and its role as the etiology of lacunar infarction is very rare [4]. Emboligenous cardiopathy especially atrial fibrillation, rheumatic valve disease, and nonbacterial thrombotic endocarditis have been reported as very infrequent causes of lacunar infarction in autopsy-based series [5]. Stroke and transient ischaemic

attack (TIA) in terms of primary and secondary prevention should be treated in the same way. We also review antithrombotic treatment in special conditions and the new anticoagulants which probably soon will replace the old ones.

Oral anticoagulation (OAC) is the treatment of choice for secondary prevention after a cardioembolic stroke [6, 7]. Warfarin is the commonest OAC used worldwide, although acenocoumarol, phenprocoumon, or anisindione are frequently prescribed in many countries. The mechanisms of action of these OAC are comparable, as they inhibit the vitamin K-dependent posttranslational carboxylation of glutamate residues on the N-terminal regions of coagulation factors II, VII, IX, and X by inhibiting the conversion of vitamin 2, 3 epoxide to reduced vitamin K [8]. Although the benefits of OAC are supported by a high degree of evidence for stroke prevention in cardioembolic entities, such as atrial fibrillation [8], they have a narrow therapeutic index, numerous drug and dietary interactions, and a significant risk of serious bleeding, including hemorrhagic stroke [9]. Alternatives to oral anticoagulation in this setting include safer and easier to use antithrombotic drugs and definitive treatment of atrial fibrillation.

2. Atrial Fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, resulting in a prevalence of about 1% in the general population [10]. The prevalence of atrial fibrillation is strongly associated with increasing age, rising to 5% in people older than 65 years and to nearly 10% in those aged 80 years [11]. AF is also the most frequent cardiac condition associated to the risk of ischemic stroke, although it is only weakly associated with transient ischemic attack (TIA) [12]. AF increases the risk of stroke 4- to 5-fold across all age groups, accounting for 10% to 15% of all ischemic strokes and nearly 25% of strokes in people older than 80 years [13, 14]. This translates to an incidence of stroke approximating 5% a year for primary events and 12% a year for recurrent events [15]. In AF associated with rheumatic heart disease, stroke risk is increased even more: 17-fold compared with age-matched controls [16]. Patients with paroxysmal and constant AF appear to have similar risks of stroke [17].

OAC therapy is highly effective in reducing stroke in patients with AF. In the late 1980s and early 1990s, 6 trials compared OAC therapy to placebo [17, 18]. Meta-analysis showed that adjusted-dose oral anticoagulation (target International Normalized Ratio (INR) 2.5; range, 2.0–3.0) is highly efficacious for prevention of all strokes (both ischemic and hemorrhagic), with a risk reduction of 68% (95% CI 50%–70%) as compared to placebo [13, 14, 19]. This reduction was similar for both primary and secondary prevention and for both disabling and nondisabling strokes. Aspirin showed a less consistent benefit for stroke prevention than anticoagulation therapy. Aspirin compared to placebo was evaluated in 3 trials, and a pooled analysis of these studies showed a mean stroke risk reduction of 21% (95% CI 0%–38%) [20, 21]. Adjusted-dose OAC resulted in a relative

risk reduction of 52% (95% CI 37%–63%) compared to aspirin [22].

In the Stroke Prevention in Atrial Fibrillation Trials (SPAF I and II), which randomly assigned patients to warfarin or aspirin (325 mg per day), multivariate analysis identified 4 atrial fibrillation subgroups with a substantial stroke rate on aspirin: patients with systolic hypertension (greater than 160), patients with impaired left ventricular function, patients with a history of prior thromboembolism, and women over 75 years in age [23]. Aspirin-treated patients with 1 or more of these risk factors had a thromboembolic rate of about 6% per year whereas those without these risk factors had a thromboembolic rate of about 2% per year.

In the SPAF Trial II, the combined use of fixed-dose warfarin (mean daily dose = 2.1 mg) with aspirin (325 mg per day) was tested as an alternative therapy to adjusted-dose warfarin (target international normalized ratio of 2.0 to 3.0) in patients with at least 1 risk factor for stroke as identified in the previous analyses [24]. The trial was stopped early when the rate of embolism was discovered to be significantly higher in the patients on the combination therapy (7.9% per year) as compared to those on adjusted-dose warfarin (1.9% per year). A meta-analysis of randomized trials comparing OAC with combined aspirin and anticoagulation at the same target INR showed an increased risk of bleeding in the combined therapy arm (odds ratio 1.43, 95% CI 1.00 to 2.02) [25]. The adequacy of aspirin prophylaxis was evaluated in Stroke Prevention in Atrial Fibrillation Trial III among patients without any of the 4 identified stroke risk factors. Stroke or systemic embolism occurred at a rate of 2.2% per year among patients taking aspirin [26]. The annual rate of stroke or systemic embolism was significantly higher in patients with a history of hypertension (more than 140 mmHg but less than 160 mmHg systolic) than in those without.

The ACTIVE W trial (Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events), which compared the efficacy of combined antiplatelet therapy (aspirin 75 to 100 mg and clopidogrel 75 mg) versus OAC in high-risk patients with AF, demonstrated clearly the superiority of OAC in the long-term prevention of major ischemic events and had a similar bleeding rate [27]. In the ACTIVE A trial, 7554 patients with AF who were considered unsuitable to receive vitamin-K antagonist therapy were randomized to receive clopidogrel (75 mg/day) or placebo added to aspirin. The addition of clopidogrel to aspirin reduced the rate of major vascular events from 7.6% per year to 6.8%, primarily due to a reduction in the rate of stroke [28]. However, the rate of major hemorrhage increased from 1.3% to 2.0% per year.

Experts conclude that warfarin therapy is indicated when the risk of stroke is high, and that aspirin is preferred when the risk of stroke is low. Several attempts have been made to establish and validate risk stratification schemes to quantify the absolute risk of stroke in patients with nonvalvular atrial fibrillation [29, 30] (Table 2). A systematic review was conducted to identify independent risk factors for stroke in patients who have AF [31]. There are 4 most consistent independent factors for stroke: prior stroke or transient ischemic attack (relative risk 2.5, 95% CI 1.8 to 3.5),

TABLE 1: Recommendations for patients with cardioembolic stroke types (AHA Guideline 2006).

Risk factor	Recommendation	Level of evidence
AF	For patients with ischemic stroke or TIA with persistent or paroxysmal (intermittent) AF, anticoagulation with adjusted-dose warfarin (target INR, 2.5; range, 2.0-3.0) is recommended. In patients unable to take oral anticoagulants, aspirin 325 mg/d is recommended.	Class I, Level A Class I, Level A
Acute MI and LV thrombus	For patients with an ischemic stroke caused by an acute MI in whom LV mural thrombus is identified by echocardiography or another form of cardiac imaging, oral anticoagulation is reasonable, aiming for an INR of 2.0 to 3.0 for at least 3 mo and up to 1 y. Aspirin should be used concurrently for the ischemic CAD patient during oral anticoagulant therapy in doses up to 162 mg/d, preferably in the enteric-coated form.	Class IIa, Level B Class IIa, Level A
Cardiomyopathy	For patients with ischemic stroke or TIA who have dilated cardiomyopathy, either warfarin (INR, 2.0 to 3.0) or antiplatelet therapy may be considered for prevention of recurrent events.	Class IIb, Level C
Rheumatic mitral valve disease	For patients with ischemic stroke or TIA who have rheumatic mitral valve disease, whether or not AF is present, long-term warfarin therapy is reasonable, with a target INR of 2.5 (range, 2.0-3.0). Antiplatelet agents should not be routinely added to warfarin in the interest of avoiding additional bleeding risk. For ischemic stroke or TIA patients with rheumatic mitral valve disease, whether or not AF is present, who have a recurrent embolism while receiving warfarin, adding aspirin (81 mg/d) is suggested.	Class IIa, Level C Class III, Level C Class IIa, Level C
Mitral valve prolapse	For patients with MVP who have ischemic stroke or TIAs, long-term antiplatelet therapy is reasonable.	Class IIa, Level C
Mitral annular calcification	Patients with ischemic stroke or TIA and MAC not documented to be calcific antiplatelet therapy may be considered. Among patients with mitral regurgitation resulting from MAC without AF, antiplatelet or warfarin therapy may be considered.	Class IIb, Level C Class IIb, Level C
Aortic valve disease	For patients with ischemic stroke or TIA and aortic valve disease who do not have AF, antiplatelet therapy may be considered.	Class IIa, Level C
Prosthetic heart valves	For patients with ischemic stroke or TIA who have modern mechanical prosthetic heart valves, oral anticoagulants are recommended, with an INR target of 3.0 (range, 2.5-3.5). For patients with mechanical prosthetic heart valves who have an ischemic stroke or systemic embolism despite adequate therapy with oral anticoagulants, aspirin 75 to 100 mg/d, in addition to oral anticoagulants, and maintenance of the INR at a target of 3.0 (range, 2.5-3.5) are reasonable. For patients with ischemic stroke or TIA who have bioprosthetic heart valves with no other source of thromboembolism, anticoagulation with warfarin (INR, 2.0-3.0) may be considered.	Class I, Level B Class IIa, Level B Class IIb, Level C
Patent foramen ovale	For patients with an ischemic stroke or TIA and a PFO, antiplatelet therapy is reasonable to prevent a recurrent event. Warfarin is reasonable for high-risk patients who have other indications for oral anticoagulation such as those with an underlying hypercoagulable state or evidence of venous thrombosis. Insufficient data exist to make a recommendation about PFO closure in patients with a first stroke and a PFO. PFO closure may be considered for patients with recurrent cryptogenic stroke despite medical therapy.	Class IIa, Level B Class IIa, Level C Class IIb, Level C

hypertension (relative risk 2.0, 95% CI 1.6 to 2.5), diabetes mellitus (relative risk 1.7, 95% CI 1.4 to 2.0), and increasing age (relative risk 1.5, 95% CI 1.3 to 1.7). The absolute rates of stroke in patients with only 1 independent risk are 6% to 9% per year for history of stroke/transient ischemic attack, 2% to 3.5% per year for diabetes mellitus, and 1.5% to 3% per year for both hypertension and age of more than 75 years. However, there is no conclusive evidence that congestive heart failure and coronary artery disease are independent risk factors for stroke.

The HEMORR₂HAGES scheme was developed by combining bleeding risk factors from previous schemes and validated to quantify the risk of bleeding in anticoagulated patients [35]. The scheme is calculated by adding 1 point

for each of the following factors: hepatic or renal disease, ethanol abuse, malignancy, old age (older than 75 years), reduced platelet counts or platelet dysfunction, uncontrolled hypertension, anemia, genetic factors, elevated fall risk, stroke, and 2 points for rebleeding (Table 3).

In primary prevention studies OAC lowered the mortality rate by 33% (95% CI 9%–51%), and the combined outcome of stroke, systemic embolism, and death by 48% (95% CI 34%–60%) [15]. In these studies, the reported annual incidence of major bleeding and intracranial hemorrhage was 1.3% and 0.3% in anticoagulated patients, compared to 1% and 0.1% in control patients. The risk of intracranial hemorrhage is significantly increased at INR values >4.0, with increasing age, and in patients with a history of stroke

TABLE 2: Stroke risk stratifications schemes in patients with nonvalvular atrial fibrillation (BP: blood pressure, DM: diabetes mellitus, CHF: congestive heart failure, TIA: transient ischemic attack, CAD: coronary artery disease, LV: left ventricular fractional shortening).

Scheme	Low risk	Moderate risk	High risk
AFI [7]	Not moderate/high risk	Age > 65, not high risk	Prior ischemia, high BP, DM
SPAF [32]	Not moderate/high risk	High BP, not high risk	Prior ischemia, female >75 yrs, CHF, LV <25%, systolic BP > 160
ACCP [10, 33]	Not moderate/high risk	1 of the following: 65–75 yrs, DM, CAD, and not high risk	Prior ischemia, high BP, CHF, >75 yrs, or ≥ 2 moderate risk factors
CHADS ₂ [14]	SCORE = +1 for CHF, high BP, DM, >75 yr, and +2 for prior stroke/TIA		
FRAMINGHAM [34]	SCORE = +6 for prior ischemia, 0 to 4 for BP, +4 for DM, +0 to 10 for age, 6 for female		

TABLE 3: Incidence of major bleeding stratified by the HEMORR₂HAGES score (data from the National Registry of Atrial Fibrillation).

HEMORR ₂ HAGES score	No. of patients	No. of bleeding	Bleeding per 100 patient-years warfarin (95% CI)
0	209	4	1.9 (0.6–4.4)
1	508	11	2.5 (1.3–4.3)
2	454	20	5.3 (3.4–8.1)
3	240	15	8.4 (4.9–13.6)
4	106	9	10.4 (5.1–18.9)
≥ 5	87	8	12.3 (5.8–23.1)
Any score	1604	67	4.9 (3.9–6.3)

[36]. From the available information it is clear that oral anticoagulation is more efficacious and more risky than aspirin to prevent first stroke in patients with AF [7]. Chronic oral anticoagulation therapy is indicated in patients with AF and high risk of stroke unless contraindicated [10, 37]. The optimal intensity of anticoagulation for prevention of stroke in atrial fibrillation patients appears to be an international normalized ratio of 2.0 to 3.0, with a target of 2.5. A case-control study found that the efficacy of warfarin declines sharply below an international normalized ratio of 2.0 [38], and the risk of major hemorrhage appears to increase significantly above an international normalized ratio of 3.0 to 4.0.

Despite the encouraging results of OAC in AF, this treatment is underutilized in clinical practice as more than one-third of eligible patients in primary care practice are not receiving it [39], and subtherapeutic INR are encountered in 45% of patients taking OAC [40].

Current guidelines for antithrombotic therapy are based on the absolute risk for stroke balanced with the estimated bleeding risk [10, 37]. In brief, if (1) no risk factors for stroke: aspirin therapy (81 to 325 mg daily); (2) 1 moderate risk factor for stroke (age over 75 years, high blood pressure, heart failure, impaired left ventricular systolic function with an ejection fraction of 35% or less, or diabetes): aspirin (81 to 325 mg) or warfarin (international normalization ratio 2.0 to 3.0, target 2.5); (3) more than 1 moderate, or any high-risk factor for stroke (previous stroke, transient ischemic attack, systematic embolism, or prosthetic heart valve): warfarin (international normalization ratio 2.0 to 3.0, target 2.5; in case of a mechanical valve, target international normalization

ratio is greater than 2.5) [10]. Alternative recommendations use the CHADS₂ scheme for risk stratification [29, 37]. Stroke-prone patients are reliably identified by a CHADS₂ score >3, and they have an average risk of 5.5 strokes per 100 patient-years on aspirin [41]. The CHADS₂ scheme is comprised of 5 conditions: recent congestive heart failure, hypertension, age of 75 years or older, and diabetes (each of which accounts for 1 point) as well as prior stroke or transient ischemic attack, which accounts for 2 points in total score calculation (Table 4).

To date, there are no randomized trials to determine the efficacy of anticoagulation treatment for different subtypes of stroke. However, there is a recommended treatment strategy for patients with atrial fibrillation presenting with stroke or transient ischemic attack [42]. In a large, multicenter, randomized study comparing rhythm- with rate-control strategy in patients with atrial fibrillation and high risk of stroke or death, rhythm-control strategy offered no survival advantage. Attempted maintenance of sinus rhythm did not reduce the risk of ischemic stroke [43]. The effect of the intensity of oral anticoagulation on the severity of atrial fibrillation-related stroke was assessed [44]. Adequate anticoagulation reduced not only the frequency of ischemic stroke but also its severity and the risk of death from stroke, highlighting an important incremental benefit of anticoagulation.

Despite its proven efficacy in secondary prevention of stroke, anticoagulation therapy is not initiated in a major portion of especially elderly patients with AF, mainly because of contraindications but also because of multiple patient and physician barriers [29]. There has been some concern about

TABLE 4: CHADS₂ score quantification of stroke risk for patients with atrial fibrillation. NRAF: National Registry of Atrial Fibrillation. From [25].

CHADS ₂ score	No. of patients (<i>n</i> = 1733)	No. of stroke (<i>n</i> = 94)	NRAF crude stroke rate per 100 patient-years	NRAF adjusted stroke rate (95% CI)
0	120	2	1.2	1.9 (1.2 to 3.0)
1	463	17	2.8	2.8 (2.0 to 3.8)
2	523	23	3.6	4.0 (3.1 to 5.1)
3	337	25	6.4	5.9 (4.6 to 7.3)
4	220	19	8.0	8.5 (6.3 to 11.1)
5	65	6	7.7	12.5 (8.2 to 17.5)
6	5	2	44.0	18.2 (10.5 to 27.4)

the risk/benefit of oral anticoagulation in elderly patients, because of a greater risk of hemorrhagic complications in this group of patients. However, the WASPO (Warfarin versus Aspirin for Stroke Prevention in Octogenarians) [45] and BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged) trials [46] have shown that OAC is safe and effective in older individuals. Therefore, there is no justification to avoid anticoagulation in very old individuals with AF, unless there is a clear contraindication.

3. Acute Myocardial Infarction

Stroke is a rare but feared complication of acute myocardial infarction (AMI) [47] that can complicate the course and outcome of those patients. The incidence of stroke during the acute phase following myocardial infarction varies considerably between studies. Rates are mostly in the range of 0.8% to 3.2%, approximately one-third occur within 24 hours following admission whereas about two-thirds occur in the first week after the myocardial infarction [48, 49]. Advanced age and AF are associated with higher risk of stroke [50, 51]. Late stroke following myocardial infarction is rare, although patients are still at increased risk during the first 1 to 2 months. The risk for stroke remained 2- to 3-times higher than expected during the first 3 years after myocardial infarction [52]. A case-control study showed that stroke secondary to AMI causes a severer neurological deficit, more unfavorable clinical course, and higher mortality than stroke in patients without a recent AMI [53]. Most ischemic strokes after AMI involve the anterior circulation and are nonlacunar [54]. Posterior circulation strokes are unusual.

Etiology of stroke after AMI can be ascribed to a common pathophysiologic process: atherosclerosis; formation of mural thrombi in areas of ventricular hypokinesis after myocardial damage and AF and cardioversion [50]. Strokes occurring several weeks after AMI may be due to chronic left ventricular thrombi, an akinetic left ventricular segment, or left ventricular dysfunction. Indeed, cerebral microembolism was detected by transcranial Doppler more often among patients with AMI with reduced left ventricular function, akinetic segments, or left ventricular thrombi [54]. For every decrease of 5% in the ejection fraction, an 18% increase in the risk of long-term stroke has been found

[55]. Inflammatory changes at the endocardial surface also enhance thrombogenicity. A systemic hypercoagulable state may promote thromboembolism early after the coronary event whereas residual fresh thrombus may enhance coagulation during the first 1 to 3 months.

Thrombolytic therapy carries a small but significant risk of intracranial hemorrhage [56–58] but the overall risk of stroke due to thrombolytic therapy in properly selected AMI patients is low compared with the impressive reduction in mortality and, thus, is associated with a favorable benefit-risk profile. Early coronary revascularization diminishes the risk of ischemic stroke with acute myocardial infarction. A delay in the acute revascularization of these patients influences the risk of perimyocardial infarction ischemic stroke independent of size of infarction or residual ventricular function [59].

Anticoagulation with full-dose heparin decreases the risk of left ventricular thrombi in patients with anterior AMI and may be effective in reducing the risk of embolization in those with left ventricular thrombi. Aspirin reduced the risk of early ischemic stroke by half in the ISIS-2 mega-trial [60]. Long-term oral anticoagulant treatment in survivors of myocardial infarction has been shown to reduce the frequency of stroke by 40% to 50% over a 3-year period [55, 61]. In patients, after AMI, anticoagulation therapy is indicated for embolic stroke prevention, and antiplatelet therapy is a matter of ongoing investigation [62, 63]. The risk of recurrent myocardial infarction, stroke, or death was significantly reduced by OAC compared to aspirin therapy in one study that allocated the antithrombotic regimens within 8 weeks of AMI or unstable angina [64]. Aspirin with medium-intensity OAC was also more effective than aspirin on its own in reduction of subsequent cardiovascular events and death. Therefore, it is recommended that OAC should be taken long term, or for at least 3 months after cardioembolic stroke due to AMI [65].

Following an acute cardioembolic stroke due to left ventricular thrombi, risk for a recurrent early embolic event is high. To decide when to start anticoagulant treatment, one has to balance the benefit of reduction in early recurrent embolism against the risk of potentiating secondary brain hemorrhage. Cardioembolic strokes have a propensity for secondary hemorrhagic transformation and, therefore, no consensus has been reached on the optimum strategy.

A greater availability of primary angioplasty should decrease stroke rates, and the introduction of newer thrombolytic agents, weight-adjusted administration of heparin, low-molecular weight heparins, and a new generation of antiplatelet drugs such as the glycoprotein IIb/IIIa receptor antagonists may also affect stroke rates as well as determinants of intracranial hemorrhage in patients with AMI [66].

4. Congestive Heart Failure

Congestive heart failure affects 4.7 million people in the United States [67]. The number of people who have had congestive heart failure is increasing, and clinical trials are trying to evaluate the optimal strategy for stroke prevention in this group. As the population ages and cardiac care improves, there is a growing number of patients living with reduced cardiac ejection fraction. The incidence of thromboembolism secondary to congestive heart failure (CHF) varies depending on the prospective or retrospective design of the studies, and whether clinical or autopsy data are assessed. Prospective studies of patients with dilated cardiomyopathy have reported a stroke incidence of 1.7 per 100 patient-years [68] while retrospective studies have given an incidence of 3.5 symptomatic events per 100 patient-years [69]. Certain groups of patients with CHF have well defined indications for chronic anticoagulation, such as previous thromboembolic event, AF, or the presence of newly formed left ventricular thrombus [70, 71]. But generally, evidence from published reports does not demonstrate convincingly that the benefits of OAC exceed the risks. The SAVE [55] and SOLVD [72] databases have shown that low-dose aspirin may be useful in preventing thromboembolism and may be less risky than OAC. In patients with underlying coronary artery disease, aspirin probably confers additional benefit. In the SAVE trial [55], aspirin use significantly reduced the risk of stroke by 56%, and the protective effect of aspirin was most pronounced in patients with a left ventricular ejection fraction <28%; in this group, aspirin use was associated with a reduction in risk of stroke of 66% ($P < .001$). Similarly, the SOLVD trial [72] showed a beneficial effect of aspirin, especially in women. The use of antiplatelet agents was associated with a 23% reduction in the risk of embolism in men and 53% reduction in women. Aspirin was also associated with a 24% reduction in the risk of sudden death [72]. The Warfarin Antiplatelet Trial in Chronic Heart Failure was designed to compare warfarin, aspirin, and clopidogrel. However, it was terminated early due to poor enrollment. Another study, "Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction," is in progress and will examine the role of warfarin versus aspirin in the primary and secondary prevention of stroke in patients with a reduced ejection fraction of less than 30% [73].

5. Valvular Heart Diseases

5.1. Rheumatic Mitral Valve Disease. Mitral valve stenosis (MS) is usually a sequela of rheumatic fever, which

afflicts approximately 1.5 million Americans. Mitral stenosis causes the left atrium to dilate and is a frequent cause of atrial fibrillation. A left atrial thrombus forms in a large number of affected patients and provides the substrate for cerebral embolism [74]. Embolism may also occur in mixed lesions of the mitral valve (stenosis-regurgitation), but isolated mitral regurgitation is not a common cause of cerebral embolism. Aortic stenosis is a rare cause of cerebral emboli, which are usually calcific.

Recurrent embolism occurs in 30 to 65% of patients with rheumatic mitral valve disease, 60 to 65% during the first year, and most within 6 months. The risk of embolization is related to age and the presence of AF [74–78]. Retrospective studies have shown a 4- to 15-fold decrease in the incidence of embolic events with anticoagulation in these patients [77, 79]. This benefit applies to both systemic and pulmonary embolism. Most trials involved patients who had 1 embolus before the onset of anticoagulation therapy [79]. However, large randomized trials have demonstrated a significant reduction in embolic events by treatment with anticoagulation in subsets of patients with AF not associated with MS [80, 81]. In these randomized trials, the subset of patients who benefited most from anticoagulation were those with the highest risk of embolic events [82, 83]. Patients with MS at the highest risk for future embolic events are those with prior embolic events and those with paroxysmal or persistent AF [76–79, 84, 85]. There are no data to support the concept that OAC is beneficial in patients with MS who have not had AF or an embolic event [86, 87]. Exceptions to OAC include pregnant women or the patient at high risk for serious bleeding [88]. In patients with recurrent embolism despite being treated with OAC at a therapeutic INR, it is recommended to add aspirin (75–100 mg/d), dipyridamole (400 mg/d), or clopidogrel (75 mg/d) [88].

5.2. Mechanical Prosthetic Heart Valves. It is well established that patients with all types of mechanical valves require antithrombotic prophylaxis for stroke prevention [89]. Lack of prophylaxis in patients with St. Jude Medical bileaflet valves was associated to embolism or valve thrombosis in 12% per year with aortic valves, and 22% per year with mitral valves [90]. For mechanical prostheses in the aortic position, the INR with warfarin therapy should be maintained between 2.0 and 3.0 for bileaflet valves and medtronic Hall valves and between 2.5 and 3.5 for other disc valves and Starr-Edwards valves; or prostheses in the mitral position, the INR should be maintained between 2.5 and 3.5 for all mechanical valves [89, 91]. The recommendation for higher INR values in the mitral position is based on the greater risk of thromboembolic complications with mechanical valves in the mitral position [89, 92–98] and the greater risk of bleeding to higher INRs [97]. In patients with aortic mechanical prosthesis who are at higher risk of thromboembolic complications, INR should be maintained at 2.5 to 3.5, and the addition of aspirin should be considered. These include patients with AF, previous thromboembolism, and a hypercoagulable state. Many would also include patients

with severe left ventricular (LV) dysfunction in this higher-risk group [99]. In older devices, such as caged ball or caged disk valve, the optimal INR for thromboembolic prevention has been higher, from 4.0 to 4.9 [94]. The combination of OAC and aspirin may be particularly useful in patients with prosthetic valves who have coronary artery disease or stroke [100]. Available data suggest that neither adjusted-dose unfractionated heparin nor fixed-dose low-molecular weight heparin (LMWH) provide adequate protection in pregnant patients with mechanical heart valves [88].

5.3. Bioprosthetic Heart Valves. In patients with bioprosthetic valves without AF, long-term therapy with aspirin (75–100 mg/d) is recommended [6, 89]. For patients with bioprosthetic valves in the mitral position OAC with a target INR from 2.0 to 3.0 is recommended during the first 3 months after valve insertion [88]. On the other hand, patients with bioprosthetic valves in the aortic position can be given either OAC (INR 2.0–3.0) or aspirin (80–100 mg/d) during the first 3 months after valve insertion [88]. In the remaining patients with associated risk factors for thromboembolism, such as AF, previous thromboembolism, or hypercoagulable condition, lifelong warfarin therapy is indicated to achieve an INR of 2.0 to 3.0. Many would also recommend continuing anticoagulation in patients with severe LV dysfunction (ejection fraction less than 30%) [99].

5.4. Mitral Annular Calcification and Aortic Valve Sclerosis. Mitral annular calcification is characterized by calcium and lipid deposition in the annular fibrosa of the mitral valve whereas aortic valve sclerosis results from similar accumulation involving the aortic valve leaflets. Mitral annular calcification and aortic valve sclerosis are associated with atherosclerosis risk factors that can promote left ventricular hypertrophy and left atrial enlargement, each of which has been reported to predict cerebrovascular events. The American College of Chest Physicians (ACCP) recommends long-term OAC in patients with mitral annular calcification complicated by systemic embolism not documented to be calcific embolism [88]. For patients with repeated embolic events despite anticoagulation therapy, or in whom multiple calcific emboli are recognized, valve replacement should be considered.

5.5. Mitral Valve Prolapse. The prevalence of mitral valve prolapse (MVP) in community-based studies is low (2.4%), and no more common among young patients with unexplained cerebral embolic events [101]. Utilizing current echocardiographic criteria for diagnosing MVP (valve prolapse of 2 mm or more above the mitral annulus in the long-axis parasternal view and other views [102], the prevalence of this entity is 1% to 2.5% of the population [103]. MVP occurs as a clinical entity with or without thickening (5 mm or greater, measured during diastasis) and with or without mitral regurgitation. Primary MVP can be familial or nonfamilial. Daily aspirin therapy (75 to 325 mg per day) is recommended for MVP patients with documented transient focal neurological events who

are in sinus rhythm with no atrial thrombi. Such patients also should avoid cigarettes and oral contraceptives. The American Stroke Association guidelines [104] recommend aspirin for patients with MVP who have experienced an ischemic stroke (class IIa, level of evidence C), based on the evidence of efficacy of antiplatelet agents for general stroke patients. No randomized trials have addressed the efficacy of selected antithrombotic therapies for the specific subgroup of stroke patients with MVP. In the current guidelines, the committee recommends aspirin for those poststroke patients with MVP who have no evidence of mitral regurgitation, AF, left atrial thrombus, or echocardiographic evidence of thickening (5 mm or greater) or redundancy of the valve leaflets. However, long-term anticoagulation therapy with warfarin is recommended (class I) for poststroke patients with MVP who have mitral regurgitation, AF, or left atrial thrombus. In the absence of these indications, warfarin is also recommended (class IIa) in poststroke patients with MVP who have echocardiographic evidence of thickening (5 mm or greater) or redundancy of the valve leaflets and in MVP patients who experience recurrent TIA while taking aspirin. In each of these situations, INR should be maintained between (2.0 and 3.0). In MVP patients with AF, warfarin therapy is indicated in patients aged greater than 65 years and in those with mitral regurgitation, hypertension, or a history of heart failure (INR 2.0 to 3.0) [105, 106]. Daily aspirin therapy is often recommended for patients with high-risk echocardiographic characteristics. Nevertheless, it is recommended that patients with MVP and stroke receive antithrombotic therapy if alternative causes of brain ischemia cannot be identified [88].

6. Cardiac Procedures

The number of patients undergoing cardiac revascularization procedures is ever increasing. Technological as well as surgical and anesthesiological advances have reduced the mortality and morbidity associated with these cardiac procedures. Neurologic complications are the leading cause of morbidity after cardiac operations.

6.1. Cerebrovascular Complications of Coronary Artery Bypass Surgery. The incidence of strokes after coronary artery bypass surgery has been reported variably depending on whether the study is retrospective or prospective; 1.5% to 5.2% in prospective studies [107–109]. Using highly sensitive diffusion-weighted MRI increases the incidence of cerebral infarctions to 18%. However, about two-thirds of these are asymptomatic [110]. Several pathophysiological mechanisms likely play a role in the causation of neurologic complications following cardiac surgery. Mechanical, thermal, hemodynamic, metabolic, infectious, and pharmacologic factors are all likely. Pathological studies of brains of patients who died after cardiac surgery reveal dilation of small capillaries and arterioles often at bifurcations. Staining with oil red O and osmium have revealed these to be due to fat microemboli numbering in the thousands. Atheromatous debris is also responsible for brain embolism during and

after cardiac surgery especially in patients with severe aortic atherosclerosis [111]; coronary bypass surgery without cardiopulmonary bypass (off-pump CABG) is theoretically associated with a lower risk of stroke, given its advantages of no aortic manipulation, no hypothermia, and no use of the cardiopulmonary bypass pump [112]. In a large study with 16,184 patients the incidence of stroke was lower in the off-pump group (2.5%) compared to the conventional CABG group (3.9%) [113]. Embolism has been implicated in the pathophysiology of stroke after on-pump CABG whereas myocardial stunning and hypoperfusion may be possible mechanisms associated with delayed onset of stroke after off-pump CABG [112]. The timely administration of platelet inhibitors and/or per-operative anticoagulation, as well as prevention of hypotensive episodes may be indicated in off-pump CABG as preventive measures against delayed onset of stroke. Yet, further studies are needed to prospectively investigate the potential benefits of pharmaceutical agents in reducing the incidence of stroke after CABG.

6.2. Cerebrovascular Complications of Left-Sided Cardiac Catheterization. Almost two-thirds of all coronary revascularization procedures are catheter-based percutaneous coronary interventions. Its frequency is growing whereas that of coronary artery bypass graft is declining relatively. Clinically relevant embolic events during diagnostic cardiac catheterization occur in 0.1% to 0.4% of patients [114]. Stroke was significantly associated with the severity of coronary artery disease (perhaps an indication of the atherosclerotic burden) and the duration of the procedure. Moreover, many embolic events occur that remain clinically silent as evidenced by the prospective study of Büsing and colleagues [115]. Using diffusion-weighted MRI studies, 15% of individuals undergoing cardiac catheterization were shown to have abnormalities indicating cerebral infarcts although they were clinically asymptomatic.

Stroke is a rare but dramatic complication of invasive cardiac procedures. In contrast to noniatrogenic stroke, the situation in a catheterization laboratory is unique because arterial access is already available and thrombolytic therapy potentially can be initiated without delay, often through the same catheter [116]. Besides intra-arterial thrombolysis, mechanical clot retrieval is also possible. Typically, patients who are preparing for cardiac transplantation are immediately anticoagulated after the implant of the left ventricular assist devices [117].

6.3. Cerebrovascular Complications of Cardiac Transplantation. Neurologic complications in heart transplant recipients in the modern era occur at a rate of 7% to 23%. Cerebrovascular complications include ischemic stroke, transient ischemic attacks, and cerebral hemorrhage. Transplantation-associated ischemic stroke is significantly more common in patients transplanted for dilated cardiomyopathy or in those with a history of prior stroke [32, 33]. Most neurologic events after heart surgery occur in a subset of patients who can be identified before the operation. In the studies by Riccotta and colleagues, 4 factors have been associated with the risk of

stroke: (1) carotid stenosis greater than 50%, (2) repeat heart surgery, (3) valve surgery, and (4) prior stroke [34, 118]. Elderly patients and women represent a strong demographic risk factor for adverse neurologic events.

7. Pacemakers

Pacemakers are needed to treat many cardiac conditions, but its presence may make the diagnosis of AF difficult. Indeed, many patients with pacemakers develop AF, and some patients with AF have concomitant sinus node dysfunction, thus requiring the use of pacemakers [119]. The lack of diagnosis of AF may lead to the omission of appropriate treatment with OAC. Thus, patients with AF after pacemaker implantation may have a 70% higher relative risk of stroke than patients without AF, even after adjustment for important clinical predictors [120]. Patients on pacemakers for sinus node dysfunction had an actuarial incidence of stroke of 3% at one year, and 5% at five years, and 13% at 10 years [121]. Pacemakers have different modes of programming and stimulation, and the incidence of AF and embolism may differ accordingly.

8. Patent Foramen Ovale (PFO)

In a significant proportion of the general population there are various forms of interatrial communication, such as patent foramen ovale, atrial septal defect, and associated disorders such as atrial septal aneurysm (ASA). Several authors have associated these disorders with paradoxical embolic phenomena and cryptogenic strokes as well as different other pathologies as migraines with aura, transient global amnesia, or the presence of “multiple ischemic brain lesions” in divers for example [122–128]. Other studies and expert opinions question these associations and emphasize that these interatrial communications are for the most part innocent bystanders [129–133]. In the Stroke Prevention: Assessment of Risk in a Community (SPARC) echocardiography study [132], PFO was not a significant independent predictor of stroke (HR 1.46, 95% CI 0.74 to 2.88). The secondary stroke prevention in patients with PFO has been evaluated in several studies. In the PFOASA (Patent Foramen Ovale-Atrial Septum Aneurysm) study, young patients (from 18 to 55 years) with cryptogenic stroke within the preceding 3 months were prospectively followed during 4 years of aspirin therapy (300 mg per day) [134]. The risk of recurrent stroke was 2.3% in patients with PFO alone, 15.2% among patients with both PFO and ASA, 4.2% among patients with neither of these cardiac abnormalities, and 0% in patients with ASA alone.

Given its prevalence in about a quarter of the normal population and that the estimated yearly risk of cryptogenic stroke in healthy people is as low as 0.1% [135], treatment in any manner because of the mere presence of an incidental PFO is unnecessary. Medical options (use of antiplatelets or anticoagulation) and surgical options (open surgical closure, minimally invasive surgery, and percutaneous devices) [136] are available for the treatment of patients after they have

suffered a cryptogenic stroke as secondary prevention. The choice of therapy depends especially on the clinical settings in which the stroke occurred (antecedent Valsalva maneuver, hypercoagulable state, and multiple strokes or events) and the morphological characteristics of the PFO (large opening, large right-to-left shunting (RLSh), RLSh at rest, and the presence of an ASA [137, 138], but making the choice of treatment modalities, especially the surgical options, is controversial. To date there are no published data on studies that have randomly assigned patients with cryptogenic stroke and PFO to different therapies. The studies so far have been observational.

For the patient with isolated PFO and a stroke or TIA, support for the use of aspirin therapy is based on 2 studies: (1) the French PFO-ASA study, which found that the risk of recurrence was only 2.3% after 4 years as opposed to 4.2% in the group with no patent foramen ovale or atrial septal aneurysm, and (2) the PICSS study (Patent Foramen Ovale in Cryptogenic Stroke Study), which did not demonstrate a statistically significant difference between the effects of (325 mg) and warfarin (INR 1.7 to 2.2) on the risk of subsequent stroke or death among patients with cryptogenic stroke and a PFO [127, 139, 140]. For those patients with a PFO and ASA, the French PFO-ASA study found the incidence of recurrent stroke with aspirin therapy to be significantly higher at 15.2% and suggested that perhaps warfarin or surgical options might be more beneficial in this cohort [127]. The PICSS study, however, refuted this finding [139]. Experts note that the PICSS study was primarily designed as a prognostic study and was underpowered to demonstrate a treatment effect [140]. And for those patients with an isolated ASA alone, the efficacy of aspirin therapy was demonstrated in the French PFO-ASA study in which the 10 patients with isolated ASA did not have a recurrence of events on aspirin therapy of 300 mg/day [127]. In the CODICIA study, 20.8% of patients received anticoagulant treatment for the prevention of recurrence. The conclusions of the CODICIA study are similar to the PICSS study: anticoagulant treatment is not significantly superior to antiplatelet therapy in the prevention of stroke recurrence. Despite the tendency to a greater benefit of anticoagulation in older patients with cryptogenic stroke, which was also observed in the PICSS study, the results and design of the CODICIA, PICSS, and WARSS studies do not justify its prolonged use at the present time [137, 138, 141]. Stroke associated with RLSh/PFO has a better functional prognosis than cryptogenic stroke without RLSh/PFO. This is due to the lesser volume of the infarct in patients with stroke and RLSh in comparison with the volume of the infarct of cryptogenic stroke without RLSh (14.3 mL (1.5–35.4) versus 6.5 mL (1.3–16.6)) and suggests that the mechanism of stroke in patients with and without RLSh/PFO is different [142].

Surgical options to close a patent foramen ovale have been offered to patients with patent foramen ovale and a history of stroke, especially when certain high-risk factors are present [138, 140]. Three surgical options for closure are available: (1) the traditional open thoracotomy foraminal closure, (2) minimally invasive surgery, and (3) percutaneous closure techniques [143]. The Randomized Evaluation of

Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) trial, the CLOSURE I trial, and the CardiaPFO trial are currently comparing medical and percutaneous closure approaches, but large patient enrolment would be necessary due to the low event rate in these patients.

Currently, the evidence is insufficient to determine if OAC is superior to aspirin for the prevention of recurrent stroke or death in patients with cryptogenic stroke and PFO, or the value of surgical or endovascular closure. Current recommendations are based mostly on expert opinion pending the completion of ongoing randomized controlled trials that are seeking to compare the various treatment modalities [138, 140, 144, 145].

9. Endocarditis

9.1. Infective Endocarditis. Cerebral embolism is a common complication of infectious endocarditis but accounted for less than 1% of all causes of cerebral embolism in the Cerebral Embolism Stroke Registry [146, 147]. Despite markedly changing risk factors, age range, and pathogenic microorganisms, there remains a striking uniformity in the frequency and distribution of neurologic problems associated with infective endocarditis. Their importance is underscored by the frequency with which they occur, the fact that they can be the initial or predominant manifestation of the disease, and that they have become a leading cause of disease mortality now that infected heart valves can be surgically repaired or replaced. In several series of patients described over a span of 6 decades, approximately 30% of patients with infective endocarditis had a neurologic complication, and for about half of those, the neurologic event was the presenting clinical symptom [148–153]. Though there has been an overall decline of mortality in patients with infective endocarditis, the morbidity from neurologic complications has remained unchanged for years.

Cerebral embolism is the most common complication occurring in 14% to 20% of patients with infective endocarditis. Cerebral emboli are considerably more common in mitral valve endocarditis than in infection of the aortic valve. About half of these emboli are multiple by neuroimaging studies. Conversion to hemorrhagic infarction occurs spontaneously in less than 10% of these patients. In developed countries, between 7% and 25% of all cases of infective endocarditis involve prosthetic valves [154]. Data pooled from multiple series of patients with prosthetic valve endocarditis show a rate of CNS complications similar to that of patients with native valve disease, provided that anticoagulation was appropriately managed.

Neurologic manifestations of infectious endocarditis mainly occur before antimicrobial treatment is begun, thus reinforcing our belief that rapid diagnosis and initiation of antimicrobial therapy may still be the most effective means to prevent neurologic complications [153]. The indications for and risk of anticoagulation for endocarditis-associated cerebral embolism continue to generate controversy. There is no convincing evidence that prophylactic anticoagulant

therapy reduces the incidence of emboli in native valve endocarditis, and it is generally believed that the routine use of anticoagulants is not justified [88]. It should neither be instated after embolism occurs because the risk of hemorrhage may be high. Patients with mechanical prosthetic valves or AF who develop endocarditis usually are continued on their anticoagulation [7]. However, the risk of hemorrhage if embolism occurs is then high. Anticoagulation should be withheld for at least 48 hours in prosthetic valve patients suffering a cerebral embolism with endocarditis. Patients with cardiogenic brain embolism should be monitored for signs of deterioration that suggest a hemorrhagic transformation, and a follow-up imaging study in 1 to 2 weeks is advisable in order to rule out abscess formation or evidence of a mycotic aneurysm [155].

9.2. Nonbacterial Thrombotic Endocarditis. Nonbacterial thrombotic endocarditis (NBTE) is reported most commonly in patients with adenocarcinoma, especially mucin-producing carcinomas of the lung or gastrointestinal tract, and lymphoma. The malignancy is usually widespread and cerebral infarction is a late complication, but in rare instances NBTE with cerebral infarction is the presenting sign of cancer. The reported incidence of systemic embolism in NBTE varies widely (14–91%, average 42%) [156]. NBTE is more common in the aortic and mitral valves, but any valve may be affected. The pathogenesis of NBTE is not fully understood, but the most important predisposing factors appear to be an underlying coagulopathy, edema, degeneration of valvular collagen, and the effects of mucin-producing carcinomas. Treatment of NBTE is directed toward control of the underlying disease, in most instances neoplasia and/or sepsis, and toward treatment of thromboembolism. The most effective agent is heparin, and little benefit has been observed with vitamin K antagonists. Patients with NBTE and systemic or pulmonary emboli should be treated with full-dose unfractionated heparin IV or subcutaneous heparin [88].

9.3. Libman-Sacks Endocarditis. Valvular involvement is the most frequent form of heart disease in systemic lupus erythematosus (SLE). Involvement includes valve masses also known as Libman-Sacks vegetations, valve thickening, valve regurgitation, and valve stenosis. On transesophageal echocardiography, the prevalence of valvular disease in SLE has been shown to be up to 60–74%. The incidence of ischemic cerebrovascular stroke in patients with SLE is 10–20%; in these patients, the existence of valvular involvement and left heart thrombi was proven in 70–90% of cases [157]. A frequent concomitant appearance of valvulopathy, thromboembolic events (mostly stroke or TIA), and antiphospholipid antibodies has been observed. Ischemic manifestations, previously thought to be due to vasculitis, are usually due to thrombotic or cardioembolic events. Because of the increased incidence of stroke in SLE and the frequent valvulopathy in these

patients, prophylactic antiplatelet therapy may be contemplated in all SLE patients. Anticoagulant treatment should be considered independently of echocardiographic results in patients who had cerebrovascular or systemic embolic events with no features of systemic SLE vasculitis [158].

10. Antithrombotic Therapy in Cardioembolic Stroke in Special Situations

10.1. Immediate Anticoagulation after Acute Cardioembolic Stroke

10.1.1. Acute Stroke. In a review of the Cochrane database system [159] twenty-four trials involving 23,748 participants with acute stroke were included. The anticoagulants tested were standard unfractionated heparin, low-molecular-weight heparins, heparinoids, oral anticoagulants, and thrombin inhibitors. For the analysis of the primary outcome, all of the data related to the initiation of anticoagulants within 48 hours of onset, and 89% of the evidence related to unfractionated heparin. Based on 11 trials (22,776 participants), there was no evidence that anticoagulant therapy reduced the odds of death from all causes (OR, 1.05; 95% CI, 0.98 to 1.12) at the end of followup. Similarly, based on 8 trials (22,125 participants), there was no evidence that anticoagulants reduced the odds of being dead or dependent at the end of followup (OR, 0.99; 95% CI, 0.93 to 1.04). Although anticoagulant therapy was associated with fewer recurrent ischemic strokes (OR, 0.76; 95% CI, 0.65 to 0.88), it was also associated with an increase in symptomatic intracranial hemorrhages (OR, 2.55; 95% CI, 1.95 to 3.33). Similarly, anticoagulants reduced the frequency of pulmonary emboli (OR, 0.60; 95% CI, 0.44 to 0.81), but this benefit was offset by an increase in extracranial hemorrhages (OR, 2.99; 95% CI, 2.24 to 3.99).

10.1.2. Acute Cardioembolic Stroke. Paciaroni et al. [160] identified randomized trials comparing anticoagulants (unfractionated heparin or low-molecular-weight heparin or heparinoids), started within 48 hours, with other treatments (aspirin or placebo) in patients with acute ischemic cardioembolic stroke. Seven trials, involving 4624 patients with acute cardioembolic stroke, met the criteria for inclusion. All studies included patients with cardioembolic ischemic stroke ($n = 4624$) randomized within 48 hours from stroke onset. Atrial fibrillation was present in 3797 patients and other mixed cardioembolic sources in 827. Three trials used UFH [161–163], 3 trials LMWH (TAIST tinzaparin, HAEST dalteparin, and FISS-bis nadroparin) [164–166], and one trial (TOAST) heparinoid (danaparoid) [167]. In the CESG (Cerebral Embolism Study Group) trial, the followup was reported only at 14 days [166]. Compared with other treatments, anticoagulants were associated with a nonsignificant reduction in recurrent ischemic stroke within 7 to 14 days (3.0% versus 4.9%, odds ratio 0.68, 95% CI: 0.44 to 1.06, $P = .09$, number needed to treat = 53), a significant increase in symptomatic intracranial bleeding (2.5% versus

0.7%, odds ratio 2.89; 95% CI: 1.19 to 7.01, $P = .02$, number needed to harm = 55), and a similar rate of death or disability at final followup (73.5% versus 73.8%, odds ratio 1.01; 95% CI: 0.82 to 1.24, $P = .9$).

In the single study in which anticoagulation was started within 3 hours from stroke onset, death or disability was reduced by anticoagulant treatment. These results should be interpreted with caution because other trials did subgroup analyses in hyperacute patients and showed neutral results. Several studies have suggested that besides its antithrombotic effects, UFH also modulates inflammation [168–172]. Thus, the positive effect of early heparin could be the result of either its antithrombotic effects and/or its modulation on the anti-inflammatory pathway that appears relevant in the first hours. Whatever the mechanism for improvement, the benefit observed in patients treated within 3 hours suggests the need for further trials on the efficacy of very early administration of anticoagulants in acute cardioembolic stroke. In selecting the study population for these trials, size of ischemia, age, and blood pressure in the acute phase, all known as risk factors for hemorrhagic complications, should be considered.

10.1.3. Acute Stroke with AF. Hart et al. presented [173] a critical review of 3 randomized clinical trials testing aspirin, heparin/heparinoid, or both involving 5029 patients with AF and acute stroke. In the International Stroke Trial (IST), 19,435 patients with suspected acute ischemic stroke within 48 hours (93% confirmed as ischemic by early CT) were randomly assigned to aspirin 300 mg/d versus no aspirin and, separately, to 1 of 2 dosages of subcutaneous heparin versus no heparin in a 2×3 factorial design [174]. Treatment was not masked, and there were no prespecified criteria for early recurrent stroke. Results for the subgroup of 3169 participants (17%) with AF have been reported. The Chinese Acute Stroke Trial (CAST) compared aspirin 160 mg/d with placebo (double-blind) in 21,106 patients with suspected acute ischemic stroke within 48 hours. AF was present in only 7% ($n = 1411$) of participants. Limited data about the subgroup of AF patients from the CAST have been published [175], with additional outcome data available combining AF patients assigned to aspirin in the CAST with those from the IST. The Heparin in Acute Embolic Stroke Trial (HAEST) randomly assigned 449 AF patients with acute ischemic stroke (all confirmed by CT) within 30 hours of stroke onset from 45 Norwegian centers to a low-molecular-weight heparin (dalteparin 100 IU/kg SC twice daily) or aspirin 160 mg/d in a double-blind design, with the main outcomes of recurrent stroke during the first 14 days and functional status or death after 3 months [176]. Early recurrent ischemic stroke occurred in about 5% of patients during the 2 to 4 weeks after initial stroke. Data from the 2 relevant randomized clinical trials conflict. The double-blind HAEST found no reduction in early recurrent ischemic stroke among AF patients randomized to receive a low-molecular-weight heparin versus aspirin [176]. In contrast, the IST found “a clear and dose-dependent reduction in recurrent ischemic stroke among patients allocated to heparin” ($P = .001$) given

subcutaneously [177]. The overall rates of recurrent ischemic stroke in the control arms (5% in IST, 8% in HAEST) and of secondary brain hemorrhage (2% in IST, 3% in HAEST) among those given heparin/heparinoid were similar in the 2 trials. However, the reduction in early recurrent ischemic stroke by heparin in the IST was almost entirely offset by increased symptomatic brain hemorrhage. Data conflict about whether early use of heparin/heparinoid reduced early recurrent ischemic stroke but are consistent regarding its lack of overall benefit on long-term functional outcome. Modest benefits for reduction of early recurrent stroke and functional outcome were associated with aspirin use, based largely on subgroup analysis from a single, large, unblinded trial.

10.1.4. When to Start Anticoagulation after a Cardioembolic Stroke for Secondary Prevention?

Subcutaneous unfractionated heparin (UFH) at low or moderate doses [174], nadroparin [178, 179], certoparin [180], tinzaparin [181], dalteparin [176], and intravenous danaparoid [182] have failed to show an overall benefit of anticoagulation when initiated within 24 to 48 hours from stroke onset. Improvements in outcome or reductions in stroke recurrence rates were mostly counterbalanced by an increased number of hemorrhagic complications. In a meta-analysis of 22 trials, anticoagulant therapy was associated with about nine fewer recurrent ischaemic strokes per 1000 patients treated (OR 0.76; 95% CI 0.65–0.88), and with about nine more symptomatic intracranial hemorrhages per 1000 (OR 2.52; 95% CI 1.92–3.30) [183]. However, the quality of the trials varied considerably. On the basis of the usual timing of secondary hemorrhagic transformation between 12 hours and 4 days after stroke onset, it seems reasonable to begin warfarin as soon as the patient is medically and neurologically stable, often 2 to 3 days after stroke, to achieve therapeutic anticoagulation 7 to 10 days after stroke onset. Some experts routinely repeat a CT scan before initiating warfarin and delay warfarin therapy if hemorrhagic transformation is evident. Minor degrees of hemorrhagic transformation are frequent (particularly on MRI), and the clinical significance regarding initiation of warfarin is unclear and controversial. No benefit of heparin has been demonstrated for acute stroke patients with AF; whether selected subgroups would respond differently remains to be proven. Aspirin followed by early initiation of warfarin for long-term secondary prevention is a reasonable antithrombotic management. Few clinical trials have assessed the risk-benefit ratio of very early administration of UFH in acute ischaemic stroke. In one study, patients with nonlacunar stroke anticoagulated within 3 hours had more self-independence (38.9% versus 28.6%; $P = .025$), fewer deaths (16.8% versus 21.9%; $P = .189$), and more symptomatic brain hemorrhages (6.2% versus 1.4%; $P = .008$) [184]. In the RAPID (Rapid Anticoagulation Prevents Ischemic Damage) trial, patients allocated UFH had fewer early recurrent strokes and a similar incidence of serious hemorrhagic events, compared with those receiving aspirin [185]. In the UFH group, ischaemic

or hemorrhagic worsening was associated with inadequate plasma levels of UFH. In view of these findings, the value of UFH administered shortly after symptom onset is still debated [186, 187].

10.2. Embolic Events during Adequate Antithrombotic Therapy. In the patient who has a definite embolic episode while undergoing adequate antithrombotic therapy or INR is in range, the dosage of antithrombotic therapy should be increased, when clinically safe, as follows: (i)warfarin, INR 2.0 to 3.0: warfarin dose increased to achieve INR of 2.5 to 3.5; (ii)warfarin, INR 2.5 to 3.5: warfarin dose may need to be increased to achieve INR of 3.5 to 4.5; (iii)not taking aspirin: aspirin 75 to 100 mg per day should be initiated; (iv)warfarin plus aspirin 75 to 100 mg per day: aspirin dose may also need to be increased to 325 mg per day if the higher dose of warfarin is not achieving the desired clinical result; (v)aspirin alone: aspirin dose may need to be increased to 325 mg per day, clopidogrel 75 mg per day per day added, and/or warfarin added [89]. However, there is class IA recommendation for European Stroke Organization not to use double antiplatelets except on special occasions like, for example, unstable angina, non-Q myocardial infarction, and after stent. When INR is in range new anticoagulants, can be used. Dabigatran is currently only approved in USA and Japan. Its use can be extended to situations of hypersensitivity, resistance or intolerance to classic anticoagulants and difficulty in daily control.

10.3. Long-Term Secondary Stroke Prevention after OAC-Related ICH. Another difficult decision in clinical practice is whether anticoagulants should be restarted and maintained indefinitely in patients with a history of OAC-related ICH and at risk of cardioembolic events. Stroke prevention in this situation needs to balance the risk/benefit of different antithrombotic options and the estimated risk of intracranial bleeding recurrence. To this aim, an important step is to establish the most likely cause of the bleeding. Whereas hypertensive vasculopathy appears to be the most important mechanism for ICH in deep hemispheric regions of the brain, cerebral amyloid angiopathy may be the most common underlying pathophysiology for lobar ICH. The risk of recurrent hypertensive ICH can be decreased by an adequate control of hypertension [188] whereas cerebral amyloid angiopathy lacks any known treatment. In a prospective study of elderly patients who survived lobar ICH, recurrent ICH occurred in 22% at 2 years [189]. The rate of recurrent ICH in survivors of deep hemispheric ICH was estimated to be 2.1% per patient-year [190]. Therefore, in patients with lobar hemorrhage and major sources of embolism, decision analysis models based on retrospective data suggest that the strategy of “do not anticoagulate” appears robust [190]. Contrarily, the risks and benefits of anticoagulation are more closely balanced when applied to patients with deep hemispheric ICH. In the latter case, OAC might be justified if the estimated risk of ischemic stroke is high.

10.4. Pregnancy. Pregnancy increases the likelihood of cerebral infarction to approximately 10-times that of the expected incidence in nonpregnant young women [191]. Cardioemboli are responsible for the majority of ischemic infarctions of arterial origin during pregnancy. Most strokes during pregnancy affect the anterior circulation, especially the middle cerebral artery. Cardiac conditions frequently associated with cerebral embolism during pregnancy include atrial arrhythmias, congenital disorders (e.g., atrial septal defects), and acquired disorders (e.g., peripartum cardiomyopathy). Venous infarction also occurs in the peripartum period [191].

The consequences of atrial fibrillation during pregnancy are potentially life-threatening. Atrial fibrillation may be chronic as a consequence of rheumatic mitral stenosis or it may develop de novo during the course of the pregnancy. Congestive heart failure occurs more frequently with de novo atrial fibrillation during pregnancy than with chronic atrial fibrillation [191]. Women with chronic atrial fibrillation or valve prosthesis who are treated with warfarin should take contraceptive precautions to avoid exposing the fetus to the potential teratogenic effect of warfarin. Warfarin (vitamin K antagonist therapy) crosses the placenta and has been associated with an increased incidence of spontaneous abortion, prematurity, and stillbirth. Warfarin can also cause bleeding in the fetus and embryopathy, consisting of nasal hypoplasia and/or stippled epiphyses after in utero exposure during the first trimester of pregnancy, and central nervous system abnormalities after exposure during any trimester. Several studies suggest that UFH or LMWH therapy is safe for the fetus [192–196]. Heparin does not cross the placenta and does not have the potential to cause fetal bleeding or teratogenicity. However, bleeding at the uteroplacental junction is possible, and numerous case series and patient registries attest to a high incidence of thromboembolic complications (12% to 24). If pregnancy is desired, alternative anticoagulation methods such as subcutaneous heparin should be implemented prior to conception and continued through the first trimester. Dipyridamole should not be considered as an alternative antiplatelet agent because of its harmful effects on the fetus. Neither warfarin nor heparin is contraindicated in postpartum mothers who breast-feed [197].

11. Bleeding Risk in Orally Anticoagulated Patients

The risk of major bleeding in patients receiving OAC is 3% per year; and approximately 20% of major bleeding events are fatal [198]. Even at safe anticoagulant levels (INR 2.0 to 3.0) annual rates of major, life threatening, and fatal bleeding are 2%, 1%, and 0.25%, respectively [199]. Every one-point rise in INR increases the risk of major bleeding by 42% [200], and the interval 2.0–2.5 gives the lowest risk of stroke and death in patients with nonvalvular AF [201]. Concomitant hypertension, prior cerebrovascular accident, gastrointestinal bleeding or anticoagulation-related bleeding, use of aspirin or nonsteroidal anti-inflammatory drugs, older

age, patient reliability, and the interactions of OAC with other medications contribute to the risk of bleeding [202].

The most frequent complication of OAC is gastrointestinal bleeding, but intracranial hemorrhage (ICH) is the main cause of fatal bleeding. In a pooled analysis of the first five trials with warfarin in patients with AF, the annual rate of OAC-related ICH was 0.3% [203]. OAC-related ICH occurs at a rate of 2 to 9 per 100,000 population/year, an incidence which is 7- to 10-fold higher than in patients not receiving OAC [204]. The incidence of intracranial hemorrhage due to OAC is increasing, probably because of the larger number of elderly patients that receive this treatment, the association with aspirin, or the expanded use of OAC for stroke prevention [205].

12. New Treatment Strategies and New Anticoagulants

Anticoagulation therapy's associated risk of hemorrhage and cumbersome monitoring requirements have encouraged the investigation of alternative therapies for individuals with atrial fibrillation. For example, indobufen, a reversible inhibitor of platelet cyclooxygenase activity, was evaluated in the SIFA trial. The SIFA trial was a prospective, randomized, open study involving a total of 916 patients with nonvalvular AF and a recent cerebral ischemic episode. Patients received either indobufen (100 or 200 mg BID) or warfarin (INR 2.0 to 3.5) for 12 months. The combined incidence of nonfatal stroke (including intracerebral bleeding), pulmonary or systemic embolism, nonfatal myocardial infarction, and vascular death was not significantly different between the two treatment groups [206]. However, the limited power of the study did not exclude the existence of substantial differences between the two treatments. Data from the AMADEUS trial, which compared the long-acting, parenteral factor Xa inhibitor, idraparin, with warfarin, showed that the idraparin arm had lower rates of stroke and systemic embolism (idraparin 0.9% versus warfarin 1.3%, $P = .007$) and was not inferior to warfarin [207]. However, idraparin had a significantly higher rate of bleeding than warfarin (19.7% versus 11.3%, $P < .0001$), especially in patients with advanced age and renal insufficiency. The BOREALIS-AF study will compare the renal dose-adjusted, biotinylated idraparin with warfarin in patients with atrial fibrillation. Other oral factor Xa inhibitors being tested for stroke prevention in patients with atrial fibrillation in phase III clinical trials include rivaroxaban in the ROCKET-AF trial [208] and apixaban in the ARISTOTLE trial.

Patients undergoing major orthopedic surgery have an elevated risk of venous thromboembolism (VTE). As a result, it has become standard practice that patients undergoing major orthopedic surgery receive thromboprophylaxis with an anticoagulant. Dabigatran etexilate and rivaroxaban, direct thrombin inhibitors, are anticoagulants that have been approved for the prevention of VTE in patients who have undergone elective total hip replacement (THR) or total knee replacement (TKR). A review from the Canadian Agency for Drugs and Technologies in Health [209] analysed the

clinical effectiveness and safety of dabigatran or rivaroxaban compared to low-molecular-weight heparins (LMWH), unfractionated heparin, warfarin, or fondaparinux for thromboprophylaxis after elective total hip replacement, elective total knee replacement, or hip fracture surgery. The studies showed no statistically significant differences between dabigatran and enoxaparin in any of the endpoints with comparable side effects and superior clinical-effectiveness of rivaroxaban 10 mg once daily compared to enoxaparin 40 mg once daily with similar side effects. However, patients with severe renal insufficiency, severe liver disease, or at high risk of bleeding were excluded from the reviewed trials [209]. Table 5 shows a comparison of different anticoagulants available [210–217].

Although their first application in clinical practice occurred in the 1940s, vitamin K antagonists remain the only form of oral anticoagulant medication approved for long-term use in stroke prevention. Vitamin K antagonists are highly effective for the prevention and/or treatment of most thrombotic disease, the significant interpatient and inpatient variability in dose-response, the narrow therapeutic index, and the numerous drug and dietary interactions associated with these agents have led clinicians, patients, and investigators to search for alternative agents. Novel anticoagulant medications are being studied for the prevention and treatment of venous thromboembolism, the treatment of acute coronary syndromes, and the prevention of stroke in patients with atrial fibrillation [218]. The direct thrombin inhibitor, dabigatran etexilate, has shown efficacy over warfarin in a recent trial for the prevention of stroke associated with AF. Rivaroxaban and apixaban are in the late stages of development and several others as edoxaban, the parenteral factor Xa inhibitor, idrabiotaparin, or the novel VKA, tecarfarin, are currently being assessed [219]. The majority of these new anticoagulants are thrombin direct inhibitors which inhibit the conversion of fibrinogen to insoluble fibrin by thrombin, binding only to the active site of thrombin and do it reversibly, inhibiting not only free thrombin but also clot-bound thrombin. They exhibit stable pharmacokinetics obviating the need for coagulation monitoring or dose titration, and lack clinically significant food or drug interaction. Moreover they offer other potential that includes fixed oncedaily dosing, oral administration and rapid onset of action. However, there are several concerns regarding potential harm from using dabigatran and rivaroxaban, including an increased risk for hepatotoxicity, clinically significant bleeding, and acute coronary events.

Ximelagatran, another direct thrombin inhibitor, was also explored in patients with AF. Two long-term studies, SPORTIF III and IV [220] (Stroke Prevention using an Oral Thrombin Inhibitor in Nonvalvular Atrial Fibrillation III (open label) and V (double-blind)) were conducted, assessing the safety and efficacy of fixed-dose ximelagatran (36 mg twice daily) compared to dose-adjusted warfarin (INR 2.0-3.0) [220, 221]. Primary events occurred in 2.3% of patients taking warfarin and in 1.6% in the ximelagatran group ($P = .1$). The rates of combined minor and major hemorrhages were lower with ximelagatran (29.8% versus 25%; relative risk reduction 14%; $P = .007$) [220]. The risk

TABLE 5: Comparison of anticoagulants. APPC: activated prothrombin complex concentrate; CYP3A4: cytochrome P450 enzyme 3A4; FFP: fresh frozen plasma; HIT: heparin-induced thrombocytopenia; Iv: intravenous; IU: international units; LMWH: low-molecular-weight heparins; PCC: prothrombin complex concentrate; P-gp: P-glycoprotein; rFVIIa: recombinant activated factor VII; Sc: subcutaneous; UFH: unfractionated heparins; *all should be used with caution with other anticoagulants, nonsteroid anti-inflammatory drugs, thrombolytics, or platelet inhibitors because of an increased risk of bleeding. ** Time to reach peak plasma concentrations and half-life elimination may be delayed after surgery; from [196–204].

Parameter	Dabigatran	Rivaroxaban	LMWH		UFH	Warfarin
			Enoxaparin	Dalteparin		
Routine coagulation monitoring required	No	No	No		At inicio	Yes
Use with renal insufficiency	Moderate: dosage adjustment (150 mg daily)	Moderate: use caution	Moderate: use caution		Moderate: yes	Moderate: use caution
	Severe: contraindicated	Severe: not recommended	Severe: dosage adjustment		Severe: use caution	Severe: use caution
Use with hepatic insufficiency	Not recommended	Contraindicated	Use caution		Use caution	Use caution
Potential for HIT	No	No	Low		High	No
Drug interactions*	Quinidine, amiodarone, antacids, potent P-gp inhibitors (e.g., verapamil, clarithromycin)	Potent inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, rifampicin). Strong CYP3A4 inducers (e.g., phenytoin, carbamazepine)	No clinically significant drug interactions known		No clinically significant drug interactions known	Multiple drugs
Reversal of anticoagulant effect	rFVIIa, APCC (in rats) [35]	rFVIIa, APCC (in rats and primates) [36, 37]	Protamine sulfate (partial)		Protamine sulfate	Vitamin K, FFP, PPC
Target	Factor Iia (thrombin) direct	Factor Xa direct	Factor Xa and Iia (thrombin) indirect		Antithrombin III	Vitamin K epoxide reductase
Route	Oral	Oral	Sc		Iv or Sc	Oral
Peak plasma levels (healthy volunteers)**	0.5 to 2 hours. After surgery: 7 to 9 hours	2 to 4 hours	3 to 5 hours 4 hours		1 to 3 hours	4 hours Therapeutic effect in 5 to 7 days
Half-life elimination**	11 after surgery: 14 to 17	5 to 9 after surgery: 7 to 11	4 to 7 3 to 4		1 to 2	20 to 60
Dosing for thromboprophylaxis after orthopedic surgery	Initial: 110 mg Maintenance: 220 mg once daily	Initial: 10 mg Maintenance: 10 mg once daily	30 mg twice daily	5,000 IU daily	5,000 units every 8 to 12 hours	Individualized once daily based on target INR 2.5

of intracranial hemorrhage was 0.19% per year for warfarin and 0.11% per year in ximelagatran, and the annual rates of ischemic strokes were 1.46% and 1.37%, respectively. Major bleeding occurred at an annual rate of 2.5% in the warfarin-treated group, and 1.9% in the ximelagatran-treated group, a nonsignificant difference. The majority of ischemic strokes were noncardioembolic in origin, typically lacunar or large-artery atherosclerosis-related strokes. However, in 6.1% of patients receiving ximelagatran, there was an increase in alanine aminotransferase greater than 3-times the upper limit of normal. In the SPORTIF V trial [221], (a double-blind trial involving relatively high-risk patients with nonvalvular AF), ximelagatran was not inferior to well-controlled

warfarin within the prespecified margin of 2.0% per year for prevention of stroke and systemic embolism. However, 3 deaths with liver failure were reported in the trials, and it was estimated 1 death from hepatic failure among 2300 patients treated [222]. In data presented to the Food and Drug Administration (FDA) on all patients receiving long-term ximelagatran, an increase in alanine aminotransferase >3x normal occurred in 7.9% of patients compared with 1.2% of patients receiving comparator therapy, leading the FDA to deny approval of ximelagatran because of concerns about hepatotoxicity [223]. Later on, the sponsor officially notified the Committee for Medicinal products for Human Use that it wished to withdraw its application for a marketing

authorization for ximelagatran for the prevention of stroke associated with AF.

In the RE-LY trial (Randomized Evaluation of Long-Term Anticoagulation Therapy) two fixed doses of dabigatran (110 mg or 150 mg, twice daily) administered in a blinded manner were compared to open-label use of warfarin in 18,113 patients with AF [224]. The primary outcome measure was stroke or systemic embolism, and the primary safety outcome was major hemorrhage. Stroke or systemic embolism occurred in 1.53% per year in patients receiving 110 mg of dabigatran, 1.11% per year with 150 mg dabigatran, and 1.69% per year in patients receiving warfarin, with a median duration of followup of 2.0 years [221]. Both doses were noninferior to warfarin, and the 150 mg dose was shown to be superior to warfarin (RR 0.66, 95% CI 0.53 to 0.82). Hemorrhagic stroke happened in 0.38% per year with warfarin, 0.12% per year with 110 mg dabigatran, and 0.10% per year with 150 mg dabigatran. Only major gastrointestinal bleeding was more frequent in patients taking 150 mg dabigatran in comparison to warfarin. In this study, there were no significant increases in liver enzymes with dabigatran [224]. The only adverse event that was more frequent with dabigatran was dyspepsia. The conclusion of this trial was that both doses of dabigatran were noninferior to warfarin in the prevention of stroke or systemic embolism. Moreover, the dose of 150 mg was superior to warfarin for embolic prevention, and the dose of 110 mg produced less hemorrhagic events. Therefore, the authors suggested that the dose of dabigatran could potentially be tailored to take into consideration the risk characteristics of a specific patient [224]. Nevertheless, it has to be taken in consideration that the number of patients needed to be treated with dabigatran at a dose of 150 mg to prevent one nonhemorrhagic stroke, in comparison to warfarin, is approximately 357 [225]. For this reason and due to a greater risk of nonhemorrhagic side effects and a twice-daily dosing, some authors think that switching to dabigatran would not be of great value in patients on warfarin with a good INR control [225].

BBC News online published on 2008 that dabigatran will cost the NHS \$4.20 per day, which is equivalent to several other anticoagulants [226], but more than ten-times the cost of warfarin. The total cost of warfarin use includes not just the cost of the actual medication, but also the time and cost of INR monitoring, which is not required with dabigatran. Dabigatran is currently approved in the USA, Canada and Japan and probably others will follow in the very near future. Its clear benefit over warfarin prompted that in many countries it is already introduced in daily practice with patients, informed consent. Failure of warfarin treatment, recurrent stroke or TIA, and poor adherence to standard treatment are some of the indications for use of this new anticoagulant.

ROCKET AF is a randomized, double-blind, double-dummy, event-driven trial, which aims to establish the noninferiority of rivaroxaban compared with warfarin in patients with nonvalvular AF who have a history of stroke or at least 2 additional independent risk factors for future stroke. Patients are randomly assigned to receive rivaroxaban, 20 mg once daily (od), or dose-adjusted warfarin titrated

to a target international normalized ratio (INR) of 2.5 (range 2.0-3.0, inclusive) using point-of-care INR devices to receive true or sham INR values, depending on the study drug allocation. The primary efficacy endpoint is a composite of all-cause stroke and noncentral nervous system systemic embolism. The primary safety endpoint is the composite of major and clinically relevant nonmajor bleeding events. Over 14,000 patients have been randomized at 1,100 sites across 45 countries, and will be followed until 405 primary outcome events are observed. The ROCKET AF study aims to determine the efficacy and safety of rivaroxaban as an alternative to warfarin for the prevention of thromboembolism in patients with AF [227].

Although some efficacy and safety data for dabigatran and rivaroxaban are available, data from additional trials and postmarketing surveillance will be needed. Alterations of rivaroxaban and apixaban pharmacokinetics upon interactions with inhibitors and inducers of CYP3A4 or P-glycoprotein may complicate the use of these compounds in daily practice whereas dabigatran elimination largely depends on renal function.

Apart from pharmacological therapy for atrial fibrillation, a broad range of surgical approaches are emerging. Traditional surgical treatment of atrial fibrillations includes the Cox-Maze III procedure [228]. New surgical approaches include alternate energy sources (radiofrequency, microwave, and cryotherapy) and simplified left atrial lesion sets. These operations cure atrial fibrillation in 70% to 80% of patients. Percutaneous left atrial appendage transcatheter occlusion (PLAATO) is an endovascular approach that is being tested for prevention of embolism in high-risk patients with atrial fibrillation who have a contraindication to anticoagulation therapy [229]. Whether mechanical measures to prevent thromboembolism prove to be as effective and safe as anticoagulation remains to be proven.

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