Oral anticoagulant therapy in the primary and secondary prophylaxis of stroke

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Stroke is the first cause of disability and the second cause of mortality in the world. Oral anticoagulants have been proved to be effective in the primary and secondary prophylaxis of stroke not only in cardiac conditions but also in other pathologies such as the antiphospholipid syndrome. Though the efficacy of oral anticoagulants in the prevention of stroke has been consolidated in several conditions such as mechanical prosthesis, atrial fibrillation, and the antiphospholipid syndrome, their role is less clear in patent foramen ovale, interatrial septal aneurysm, dilated cardiomyopathy, and aortic plaques. Nevertheless, oral anticoagulants have recently been re-evaluated in large clinical trials and have been shown to be effective in the secondary prevention of myocardial infarction and stroke. This review considers both the established and controversial aspects and the role of anticoagulation clinics in the practical approach to these patients, as well as their education and quality of life.

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Introduction

As a clinical entity, stroke is complex from several points of view: the pathogenic, the clinical, the prognostic, and the therapeutic. In the United States, the annual incidence of stroke is close to 700 000 events[1] and it increases with age[2]. In Europe, the incidence of stroke ranges from 252/100 000/year among males aged 55-59 years to 3813 for males aged > 90 years and from 86 to 4321 in age-matched women[3]. In Italy the incidence for a first event in subjects aged 65-84 years is 9.51 (95% confidence interval-CI 7.75-11.27) per 1000/person/years with a prevalence of 4.6-7.4% from Florence to Naples. These data are derived from the Italian Longitudinal Study on Aging (ILSA), which estimates an annual expectance of 153 000 new cases[4]. In the Italian population < 45 years, the incidence of stroke is about 10/100 000 with 3300 new cases each year[5]. Stroke represents the first cause of severe disability and the third cause of death in the United States[2], in Europe and in Italy[3], while in a recently published report it appears to be the second cause of mortality worldwide[6]. Stroke is responsible for 9.5% of all deaths and for 5.1 of the 16.7 million deaths due to cardiovascular disease[7]. Among 80% of the patients who survive, the risk of recurrence is higher during the first few weeks: about 10% during the first year and 5% per year later[6]. In 80% of patients stroke is ischemic in origin[8]. Ischemic stroke, which can be identified and divided into five classes on the basis of risk factors, clinical grounds and laboratory investigation (TOAST criteria)[9], is cryptogenic in 30-40% of cases[10]; a possible cardiac mechanism could be involved in the pathogenesis of a significant amount of cases. Although it is difficult to determine the exact frequency of cardioembolic stroke, as about one third of the patients with a possible source of cardioembolism presents concomitant cerebrovascular disease[8], it has been estimated to account for about 25% of all ischemic strokes; it is particularly common in the elderly (> 70 years), and it is associated with the worst prognosis and with a low percentage of early recurrence[11]. The aim of this review is to evaluate the impact of oral anticoagulant therapy (OAT) in primary and secondary antithromboembolism prophylaxis not only in cardiac conditions but also in various pathologies associated with an increased risk of ischemic stroke. The management and the quality of life of patients treated with OAT will also be briefly discussed in this review.

Atrial fibrillation

Atrial fibrillation is the most common arrhythmia in the elderly and is a powerful

risk factor for stroke. The prevalence in the general population approximates 0.5-1.0%[12] but it increases with age: 2-3 new cases per 1000 per year for the population aged between 55 and 64 years to 35 new cases per 1000 per year for the population aged between 85 and 94 years[13]. Non-valvular atrial fibrillation (NVAF) is associated with an approximately 5-fold risk for stroke compared to sinus rhythm; it has an incidence of 4.5% per year[14]. About 16% of ischemic strokes are associated with atrial fibrillation, while about 10% are probably caused by embolization from thrombi in the left appendage. Echocardiography shows thrombi in the left appendage in 10% of the patients with NVAF, and in 20-40% of those with NVAF who suffered from a recent thromboembolic episode[15]. Other than stasis in the left atrium and in particular in the left appendage[16], it has been proposed that hypercoagulability and the association with atherosclerosis play a role in the pathogenesis of thromboembolism. An increase in the indicators of platelet activation, factor Xa, thrombin and fibrinolytic activity has been found[17,18] but conflicting results have also been reported[19]. Hypercoagulability may therefore be a marker of underlying atherosclerotic disease.

The role of the most common mutations, nowadays considered as risk factors for deep vein thrombosis (factor V Leiden and G20210A), has recently been studied in patients suffering from atrial fibrillation. While factor V Leiden is not associated with thromboembolism in this population[18], an increased risk for stroke (odds ratio-OR 3.3, 95% CI 1.1-9.6) has been found in patients with atrial fibrillation and the G20210A mutation[20]. Accordingly, for cardioembolism we may suppose a pathogenesis similar to that for deep vein thrombosis: stasis and, if this mutation is present, hypercoagulability may play a synergic role. These findings could have important practical consequences when deciding whether or not to place a patient, that is, with age as the only risk factor, on anticoagulants or for a better stratification of the individual risk.

In fact, for NVAF the identification of risk factors for thromboembolism is important because it permits an individualized antithrombotic prophylaxis based on the risk of stroke.

Consistent independent predictors of ischemic stroke in NVAF are: advanced age (> 75 years), hypertension, previous stroke, systemic embolism or a transient ischemic attack (TIA) and left ventricular dysfunction with an ejection fraction < 25% (high risk factors). Age between 65 and 75 years, diabetes mellitus and coronary artery disease or previous myocardial infarction are possible predictors[21] (moderate risk factors).

Many studies have been carried out to verify the efficacy and safety of oral anticoagulants and aspirin in the prophylaxis of stroke in atrial fibrillation. According to the results of a meta-analysis published in 1999, adjusted-dose warfarin reduced stroke by 62% (95% CI 48-72%) and ischemic stroke by 65% (95% CI 52-74%); aspirin reduced stroke by 22% (95% CI 2-38%) and ischemic stroke by 23% (95% CI 0-40%); warfarin was more efficacious than aspirin (relative risk reduction 36%, 95% CI 14-52%)[22]. A comparison between warfarin and aspirin has been evaluated further in a recent meta-analysis that showed that oral anticoagulants reduced the risk of ischemic stroke by about 50%[23]. However, the risk of major bleeding was higher for patients treated with warfarin, the hazard ratio being 1.71. From a practical point of view, treating 1000 patients for a year with oral anticoagulants rather than aspirin would prevent 23 ischemic events while causing 9 additional major bleeding episodes. The SIFA (Studio Italiano Fibrillazione Atriale) study compared adjusted-dose warfarin with indobufen: there was no significant difference in the incidence of stroke, myocardial infarction, pulmonary embolism or vascular death (9% warfarin, 10.6% indobufen), but OAT was associated with a higher frequency of bleeding episodes (5.1% warfarin, 0.6% indobufen)[24]. The SIFA II is an ongoing study undertaken to evaluate the efficacy and tolerability of indobufen versus aspirin in the primary and secondary prevention of stroke in NVAF.

The recommendations of the FCSA (Italian Federation of Anticoagulation Clinics) for the antithrombotic prophylaxis of stroke with oral anticoagulants have recently been published in a guide[25]. Just as those of the Sixth ACCP (American College of Chest Physicians) Consensus Conference[26], they are based on a risk stratification which takes into consideration high, low, and moderate risk patients. Oral anticoagulation (target INR 2.5) is indicated in patients with at least one high risk factor or two moderate risk factors. In the presence of one moderate risk factor one may choose between oral anticoagulants and aspirin. Aspirin (325 mg/day) should be considered in patients aged < 65 years without high or moderate risk factors. In this guide the positive hemorrhagic profile, which may have a role in the evaluation of patients for anticoagulation, has been defined: family history positive for severe hemorrhage or a personal history positive for previous cerebral bleeding, cerebral angiomatosis, recent major bleeding and a recent diagnosis of genito-urinary and gastrointestinal tract pathologies with a bleeding risk (in particular diagnosis of peptic ulcer in the last 5 weeks). The American Heart Association (AHA)[27] and the European Society of Cardiology (ESC)[28] recommend oral anticoagulation (INR 2.0-3.0) in the presence of heart failure, a left ventricular ejection fraction < 35%, thyrotoxicosis and hypertension. A higher degree of anticoagulation (INR 2.5-3.5) is recommended in patients with prior thromboembolism and persistent atrial thrombus. In patients > 60 years with diabetes mellitus or coronary artery disease, aspirin (81-162 mg/day) could be added to warfarin (target INR 2.5); a lower intensity anticoagulation (target INR 2.0) is recommended in subjects, particularly women, who are > 75 years.

Aspirin (325 mg/day) is the treatment of choice in the other cases.

Older persons with atrial fibrillation represent a particular category of patients. As a matter of fact, the attributable risk of stroke in patients with atrial fibrillation increases with age from 1.5% in 50-59 year-old patients to 23.5% in 80-89 year olds[14]. Therefore, in the absence of contraindications, an individual > 75 years with atrial fibrillation should be anticoagulated. On the other hand, the ISCOAT (Italian Study on Complications of Oral Anticoagulant Therapy) study shows that major bleeding is more frequent in subjects > 75 years (5.1% per year) than in younger individuals (1% per year). Moreover, multivariate analysis of the factors related to spontaneous major bleeding (age > 75 years, female sex, diabetes, and previous thromboembolism) demonstrates that only advanced age is independently associated with an increased risk of such episodes (relative risk 6.6, 95% CI 1.2-37)[29]. Nevertheless, another study shows that the quality of oral anticoagulation and the incidence of bleeding were similar in the group of patients > 75 years and in the control group (60-69 years old)[30]. Consequently, the decision of whether or not to anticoagulate an old patient with atrial fibrillation should be taken on an individual basis, and the possible presence of other thromboembolic risk factors, previous episodes of bleeding and the individual compliance should also be taken into consideration.

Pharmacological or electrical cardioversion is advisable in very symptomatic patients with atrial fibrillation and in those with relatively recent-onset atrial fibrillation (< 12 months) even when the symptoms are mild[31]. A study on 570 under-65 and 582 over-65 patients showed that age did not predict the success of cardioversion nor did it predispose to a higher complication rate[32]. Left atrial enlargement reduces the probability that sinus rhythm be maintained in the long term[33]. However, no absolute left atrial size should preclude any attempt at cardioversion, particularly in case of a first episode of atrial fibrillation and when the duration of this arrhythmia is relatively brief (weeks)[34]. A high left atrial appendage flow velocity identifies patients with a greater likelihood that sinus rhythm after successful cardioversion be maintained in the long term[35,36]. Two recently published studies have demonstrated that cardioversion compared with the rate control did not offer significant advantages in terms of mortality, heart failure, thromboembolic complications, bleeding, hospitalization, and adverse drug effects[37,38]. However these studies have enrolled patients aged > 60 years most of whom suffered from recurrent/persistent atrial fibrillation. The results of these studies should therefore be interpreted with caution since the restoration and maintenance of sinus rhythm remain the primary targets in symptomatic and young patients with a first episode of atrial fibrillation. The risk of systemic cardioversion-related embolization without anticoagulation is 5-7% but is reduced to 0-1.6% by anticoagulant therapy[39]. In case of atrial fibrillation lasting > 2 days, anticoagulation should be administered for 3 weeks before elective cardioversion and for 4 weeks after successful cardioversion, even though randomized controlled trials have not been performed[26].

El Gendi et al.[40] think that cardioversion of an atrial fibrillation lasting < 48 hours is not safe without echocardiographic guidance; in fact, thrombi form within a few hours of the development of atrial fibrillation in some patients, and are found in 14% of patients with acute atrial fibrillation[41]. Since an atrial thrombus may persist and remain mobile for some weeks despite anticoagulation, follow-up transesophageal echocardiography should be recommended in patients with evidence of atrial thrombi and in whom cardioversion is being considered[39].

Because the recurrence of post-cardioversion atrial fibrillation is more frequent during the first 3 months[13], El Gendi et al.[42] do not think it is safe to administer anticoagulants for only 4 weeks after cardioversion. In a recently published study comparing the rate and rhythm control in patients with atrial fibrillation, the majority of strokes occurred after warfarin had been withdrawn[37]. The recently published guidelines on OAT by FCSA[25] suggest that anticoagulation extended to at least 3 months after cardioversion would be more prudent. Finally, percutaneous left atrial appendage transcatheter occlusion could be an important tool in the future for the prevention of stroke in patients with contraindications to anticoagulation[43].

In summary, warfarin (INR 2.0-3.0) is recommended in patients with one major risk factor (previous stroke, TIA or systemic embolism, hypertension, low ejection fraction or age > 75 years) or two or more minor risk factors (age between 65 and 75 years, diabetes or coronary artery disease). Aspirin (325 mg/day) or warfarin (INR 2.0-3.0) could be administered in the presence of only one minor risk factor. Aspirin is the treatment of choice in the absence of risk factors. For patients who can undergo cardioversion, oral anticoagulation (INR 2.0-3.0) is indicated for 4 weeks before and for 12 weeks after rhythm control.

Mechanical heart valves

Patients with mechanical heart valves must be placed on anticoagulant therapy.

The incidence of thromboembolic events, almost all cerebral, during anticoagulation therapy is 0.71 per 100 patient-years; this risk is greater in female patients and increases with age. It varies according to the position and type of valve[44]. As a matter of fact, first generation prostheses, such as the Starr Edwards caged ball and Bjork-Shiley standard valves, have a high thromboembolic risk; single tilting disk valves, such as Medtronic Hall, have an intermediate risk; a low risk is associated

with the newer bileaflet valves (St. Jude Medical, Sorin Bicarbon and Carbomedics)[45].

Which anticoagulation target is recommendable in these patients? The authors of the above study[44] recommended a target INR of 3.0 to 4.0. In fact, the incidence of both thromboembolic and bleeding complications was the lowest when the INR was between 2.5 and 4.9.

Pengo et al.[46] demonstrated that moderate intensity anticoagulation (target INR 3) caused a significantly lower number of major and minor bleeding events compared to moderate-high intensity treatment (target INR 4); the rate of thromboembolism did not differ between the two groups.

The AREVA trial is a multicenter randomized study that compared moderate oral anticoagulation (INR 2.0-3.0) with the usual regimen (INR 3.0-4.5) after a single prosthesis replacement. Moderate anticoagulation was as effective as conventional treatment in preventing thromboembolism and reduced the incidence of bleeding. However, the patients enrolled in this study were low-risk subjects (in sinus rhythm and with a mean left atrial diameter ≤ 50 mm), and most of them (95%) had an aortic valve (in itself associated with a lower cardioembolic risk)[47].

As regards the combination of anticoagulants with aspirin, the addition of aspirin to warfarin in 370 patients with mechanical heart valves or high-risk patients with tissue valves (atrial fibrillation or a history of thromboembolism) reduced mortality due to vascular causes and major systemic embolism (1.9% per year in aspirin-treated patients versus 8.5% per year in placebo-treated patients; risk reduction with aspirin 77%; 95% CI 44-91%). However, aspirin significantly increased the overall risk of hemorrhagic complications but not of severe bleeding[48]. Another study demonstrated that the combination of low-intensity oral anticoagulants (INR 2.5-3.5) plus aspirin and high-intensity oral anticoagulants alone (INR 3.5-4.5) offer similar antithrombotic protection, without an increase in bleeding[49].

On the basis of these findings, the Sixth ACCP Consensus Conference[50], the AHA[51] and the ESC[52] have recommended warfarin with a different intensity of anticoagulation in proportion to the thromboembolic risk associated with different types and positions of the prostheses. In particular, patients in sinus rhythm with a mean left atrial diameter ≤ 50 mm and with a tilting or bileaflet aortic valve should be anticoagulated with a target INR of 2.5[47]; if in these patients atrial fibrillation is present, the recommended target INR is 3.0, otherwise aspirin (80-100 mg) could be added to oral anticoagulants (target INR 2.5)[50]. The mechanical valves (tilting disk and bileaflet) in the mitral position require a target INR of 3.0[46]. The patients with a caged ball or caged disk should be anticoagulated with a target INR of 3.5[44] or treated with the combination of oral anticoagulants (INR 2.5-3.5) plus aspirin (80-100 mg); this approach is also recommended for patients with a mechanical prosthesis in the presence of coronary artery disease, stroke or previous thromboembolism despite anticoagulant treatment[50,51].

In summary, OAT (target INR 2.5) is recommended for tilting disk (Medtronic Hall) or bileaflet (Carbomedics or St. Jude Medical) mechanical valves in the aortic position in patients in sinus rhythm and without atrial dilation; in the presence of atrial fibrillation, such patients could be treated with oral anticoagulants (target INR 3.0) or by adding aspirin (80-100 mg/day) to warfarin (target INR 2.5). A target INR of 3.0 is recommended for patients with tilting or bileaflet mitral valves. For first-generation caged ball or caged disk valves (Starr Edwards and Bjork-Shiley) the recommended target INR is 3.5; an alternative approach could be a combination of aspirin (80-100 mg/day) and oral anticoagulants (target INR 3.0). This association should also be indicated for high-risk patients (coronary artery disease, stroke or previous embolism despite anticoagulation).

Valvular heart disease

Among the valvular heart diseases we distinguish between mitral and non-mitral valve disease. The former includes mitral regurgitation, mitral valve prolapse and mitral stenosis whereas the latter includes aortic stenosis and aortic regurgitation. The cardioembolic risk is clearly different.

In a recent study[53] severe aortic stenosis was an independent predictor of cerebrovascular events (relative risk 3.5, 95% CI 1.4-8.6); however, the authors did not distinguish the subtype of stroke (cardioembolic or macroangiopathic), and aortic valve disease could be a marker of diffuse atherosclerotic disease rather than a cardioembolic source. Thus, in the absence of conditions that require anticoagulation with a target INR of 2.5 (previous cardioembolism, cardiac failure[45], atrial fibrillation or mitral valve disease[54]), according to the ESC[55] and AHA[51], antithrombotic therapy is not indicated for patients with isolated aortic valve heart disease.

Significant mitral regurgitation may play a protective role against the formation of left atrial spontaneous echocontrast and/or thrombi[56]. In 105 patients in sinus rhythm the prevalence of a left atrial thrombus was 0% for predominant mitral regurgitation and 14.3% for predominant mitral stenosis ($p < 0.0001$)[57]. Warfarin is not recommended in isolated mitral regurgitation; however, it must be used in the presence of other conditions (such as paroxysmal or permanent atrial fibrillation[51], previous embolism[54], left atrial thrombus[55] and cardiac failure with a low ejection fraction[45]) that predispose to cardioembolism.

Mitral stenosis is associated with a prevalence of thromboembolism of about 20%[58,59] with an incidence of 1.5% per year[60]. The cardioembolic risk in the pres-

ence of atrial fibrillation is 2-7 times greater[60,61]. Consequently, in the long term patients with mitral stenosis and atrial fibrillation should be anticoagulated with a target INR of 2.5; however, this recommendation derives from large studies on NVAF. Pengo et al.[62] have recently shown that even a lower-intensity anticoagulation (target INR 2.0), compared to a higher-intensity anticoagulation (target INR 3.0), is effective and safer in patients with mitral stenosis and atrial fibrillation. However, this is the only published study that addresses this topic and the issue needs to be confirmed. It is more difficult to decide when mitral stenosis is associated with sinus rhythm. However, predictors of systemic embolism are a larger left atrium, older age[63] and left atrial spontaneous echocontrast[61,63]. Only a few studies[64,65] show that the degree of stenosis is related to an increased risk of embolization. Mitral stenosis in sinus rhythm should therefore be anticoagulated in the presence of: atrial dilation (≥ 55 mm for the ACCP[54] and the AHA[51], ≥ 50 mm for the ESC[55]), spontaneous echocontrast or thrombus in the left atrium or appendage[45] and previous embolism[51]. In other cases of mitral valve disease in sinus rhythm, clinicians should decide whether or not to anticoagulate the patient on the basis of individual risk factors such as advanced age, atrial dilation, and the severity of the lesion[54]. Although in some studies[66,67] mitral valve prolapse has been reported to be associated with cerebral ischemia, others have not been able to confirm an important role for cardioembolism[68,69]. Aspirin is empirically suggested in patients who have had a TIA, but should in any case be given to patients in these conditions with or without mitral valve prolapse[54]. Oral anticoagulants (target INR 2.5) are therefore recommended only in patients with a history of stroke, repeated episodes of TIA despite aspirin treatment or a cardioembolic event[51,54]. Just as for NVAF, if atrial fibrillation is concomitantly present the choice between aspirin and oral anticoagulants depends on the individual risk factors for cardioembolism. In terms of clarity the position of antithrombotic treatment in patients with mitral annular calcification is even worse[70,71]. No evidence exists that oral anticoagulants should be used in patients with this condition alone. The same also holds true for aspirin. Warfarin is indicated in the presence of atrial fibrillation or systemic, but not calcific, embolism[54].

In summary, aortic valve disease does not require anticoagulation in the absence of other indications (atrial fibrillation, previous cardioembolism, heart failure or mitral valve disease). OAT (target INR 2.5) is recommended for mitral regurgitation associated with atrial fibrillation, previous embolism, a left atrial thrombus or a low ejection fraction. Patients with mitral stenosis and atrial fibrillation should be anticoagulated with a target INR of 2.5. Mitral stenosis in sinus rhythm requires anticoagulation (target INR 2.5) in the presence of: atrial dilation (≥ 50 mm), previous embolism and left atrial spontaneous echocontrast or thrombus. Oral anticoagulants (target INR 2.5) are indicated in mitral valve prolapse associated with atrial fibrillation, stroke or systemic embolism and multiple TIAs despite aspirin treatment. Mitral annular calcifications require anticoagulation (target INR 2.5) if associated with atrial fibrillation or systemic, but not calcific, embolism.

Myocardial infarction

Cerebrovascular diseases are strongly associated with cardiac disease; during 8.2 years of follow-up, 8.1% of the 3122 patients with stable coronary disease developed cerebrovascular events, mostly ischemic (95%). The degree of severity of angina pectoris predicts an increased risk for subsequent ischemic stroke[72].

The cardioembolic risk is greater during the first few weeks after an acute myocardial infarction; during the first 2 weeks the incidence of stroke ranges between 0.7 and 4.7%. The extent of myocardial damage, the degree of left ventricular dysfunction and the detection of mural thrombi at echocardiography are risk factors for cerebral and peripheral thromboembolism during the period soon after infarction; advanced age and a decreased ejection fraction are independent predictors of an increased risk for stroke for 5 years after an acute event[73]. A meta-analysis reported by Anand and Yusuf[74] in 1999 shows that, compared with placebo, high-intensity (INR 2.8-4.8) and moderate-intensity (INR 2-3) anticoagulation significantly reduce the risk for a cerebrovascular event, both hemorrhagic and non-hemorrhagic (respectively, OR 0.52, 95% CI 0.40-0.68 and OR 0.47, 95% CI 0.27-0.81), in patients with coronary artery disease. Considering only ischemic stroke, the results of the Sixty Plus Reinfarction[75], WARIS[76], and ASPECT[77] studies demonstrate that, compared to placebo, high-intensity anticoagulation reduces the risk significantly (OR 0.35, 95% CI 0.26-0.48).

After the two studies that denied the role of warfarin in the secondary prophylaxis of myocardial infarction (CARS[78] and CHAMP[79]), two new studies have recently been published on the subject. In the WARIS II[80] study, the incidence of death, non-fatal reinfarction, and cerebral stroke in patients after acute myocardial infarction was 20% in the group treated with aspirin alone (160 mg/day), 16.7% for the patients treated with warfarin alone (INR 2.8-4.2), and 15% for those who received a combination of aspirin (75 mg/day) and warfarin (INR 2.0-2.5). In particular, thromboembolic stroke events were significantly more reduced both by warfarin alone (1.4%) and by warfarin plus aspirin (1.4%) compared to aspirin (2.6%, OR 0.52, 95% CI 0.28-0.97). Even though the number of events was small, these findings indicate a positive effect of warfarin on the primary prophylaxis of thromboembolic stroke in patients with atherosclerosis. The ASPECT-2[81] study, which enrolled far fewer patients, showed a re-

duction in cardiovascular events and death, but the number of stroke events recorded were too few to draw any final conclusions. Why were the results of CARS and CHAMP so different from those of WARIS II and ASPECT-2 taken together? Probably because in CARS and CHAMP warfarin was administered in low doses and hence its effects were reduced. In conclusion, although aspirin is the treatment of choice, oral anticoagulants seem more effective in preventing thrombosis in atherosclerotic patients. Therefore, their role in preventing ischemic stroke, regardless of whether or not it was thromboembolic in origin, in patients with myocardial infarction could be re-evaluated. Actually, in agreement with the recommendations of the Sixth ACCP Consensus Conference[82] and with other later ones published by the AHA in 1999[83], long-term oral anticoagulation is recommended for patients who do not tolerate aspirin and for those with myocardial infarction and atrial fibrillation. Warfarin for 1-3 months is indicated for patients with anterior myocardial infarction (high cardioembolic risk) and for those with myocardial infarction if complicated by a low ejection fraction, mural thrombi and previous embolism. However, the members of the ESC recommend the use of oral anticoagulants only in patients who do not tolerate aspirin[84]. In the light of the recent studies on the combined use of oral anticoagulants (target INR 2.5) and aspirin, future recommendations will probably take this approach into account. Such an approach is particularly relevant for patients with recurrent ischemia.

In summary, long-term anticoagulation (INR 2.0-3.0) is recommended in patients with myocardial infarction and atrial fibrillation; warfarin for at least 3 months in anterior myocardial infarction and in myocardial infarction complicated by severe left ventricular dysfunction, thrombosis or previous embolism. Combined oral anticoagulation and aspirin for patients with previous myocardial infarction and recurrent ischemia.

Dilated cardiomyopathy

The factors that predispose to thromboembolism in patients with cardiomyopathy are the following: a) reduced contractility, b) regional wall motion abnormalities (reduced wall motion), c) association with atrial fibrillation[85].

The incidence of stroke in patients with dilated cardiomyopathy secondary to myocardial infarction is 1.5/100 patients/year, while the rate of stroke during the 5-year-follow-up is 8.1%. In particular, after myocardial infarction patients with an ejection fraction of ≤ 28% showed a relative risk of stroke of 1.86 (95% CI 1.15-3.04) when compared to patients with an ejection fraction of ≥ 35%. Independent risk factors for stroke were older age, ejection fraction, and lack of treatment with aspirin or oral anticoagulants. The latter appears to be the most important (relative risk 0.19, 95% CI 0.13-0.27)[73]. A retrospective study that considered the database of 6378 patients studied in SOLVD (Studies of Left Ventricular Dysfunction) showed a higher annual incidence of thromboembolism in women than in men (2.4 vs 1.8%). Multivariate analysis confirmed these findings indicating an association between a decline in the ejection fraction and thromboembolic risk in women but not in men (relative risk per 10% decrease 1.53, 95% CI 1.06-2.20)[86]. The SOLVD database was also useful to evaluate the effects of oral anticoagulation on the mortality and morbidity of patients with left ventricular dysfunction. This study showed that oral anticoagulation confers a reduction in total mortality (adjusted hazard ratio 0.76, 95% CI 0.65-0.89) but not in fatal stroke[87]. Again, in the SAVE trial (Survival and Ventricular Enlargement) OAT was effective in reducing the risk of stroke by 81%[73]. However, in these studies, since OAT was non-randomized, its intensity was not well monitored. The ACCP, AHA, and ESC do not provide specific recommendations for this condition[10,88]; however, we think that oral anticoagulation (target INR 2.5) should be considered when cardiomyopathy is associated with atrial fibrillation and previous thromboembolism[89]. Women with an ejection fraction < 25% should also be treated with oral anticoagulants. Although there are no solid data for treating men only with an ejection fraction < 30% (the relative risk does not reach significance but the incidence of thromboembolism is increased), it seems wiser to consider oral anticoagulation on a case-by-case basis.

In summary, long-term anticoagulation (INR 2.0-3.0) is recommended in patients with dilated cardiomyopathy associated with atrial fibrillation and previous cardioembolism or in women with an ejection fraction < 25%.

Patent foramen ovale and interatrial septal aneurysm

Interatrial septal abnormalities such as patent foramen ovale and interatrial septal aneurysm are frequently found in young subjects with cryptogenic cerebral infarction. A pathogenic relationship among patent foramen ovale, interatrial septal aneurysm and stroke has not yet been well established. Paradoxical embolism from a deep vein thrombosis or a mural thrombus in the aneurysm itself may play a role in this regard. Another possibility takes into account the formation of thrombi caused by atrial arrhythmias such as paroxysmal atrial fibrillation or atrial flutter[90]. In the general population patent foramen ovale has a prevalence of 22-26%[91], while the prevalence of interatrial septal aneurysm is < 1%[92]. A diagnosis of interatrial septal aneurysm is made when the septum appears to be abnormally redundant, mobile, and when it presents an excursion > 10 mm beyond the septum plane in the

right or left atrium or in both[92]. Patent foramen ovale is usually diagnosed with a contrast medium, obtained by mixing 0.5 ml of air with 4 ml of saline and 0.5 ml of blood in a syringe to produce an emulsion of microbubbles that can easily be detected at ultrasound[93]. Transesophageal echocardiography is probably the most sensitive technique for the diagnosis of patent foramen ovale[94] though it is expensive and rather invasive to carry out immediately after a stroke. Transcranial Doppler seems to be a cost-effective and sensitive procedure that may easily be used as a screening test in patients in whom paradoxical embolism is suspected[91]. However it has some limitations since a number of methodological parameters can affect the procedure. These include: the timing of the Valsalva maneuver, the dose and the type of contrast medium, i.e. agitated saline with air microbubbles or a galactose-based agent, and the patient's posture during the examination[95-97]. As reported by a recent meta-analysis[98], both patent foramen ovale and interatrial septal aneurysm are considered independent risk factors for embolic stroke although Mas et al.[99] did not find any role for interatrial septal aneurysm in this regard. Quite recently Mattioli et al.[100] have reinforced the role of interatrial septal aneurysm as an independent risk factor for stroke in patients aged < 55 years. The risk of stroke is even more increased in case of the concomitance of both patent foramen ovale and interatrial septal aneurysm in patients < 55 years, as reported in a meta-analysis of two case-control studies in which the OR was > 15 though with wide CI (2.83-85.87)[98]. Finally, in a recent large retrospective Italian study the prevalence of patent foramen ovale and interatrial septal aneurysm or both was significantly higher in patients with a recent TIA/stroke compared to subjects who underwent a transesophageal echocardiography for other indications[101]. Moreover, a possible role for thrombophilia (G20210A mutation of prothrombin gene) has recently been recognized in these patients[102]. It seems crucial to quantify the shunt size, since a larger patent foramen ovale is more likely to be the cause of paradoxical emboli than a smaller one[103,104]. Serena et al.[105] also reported an increased risk for cryptogenic stroke (OR 12.4, 95% CI 4.08-38.09) when the right-to-left shunt showed > 25 signals. In patients with asymptomatic patent foramen ovale, OAT is not recommended for the primary prophylaxis of ischemic stroke, but the same holds true for secondary prophylaxis too. This is due to a lack of dedicated clinical trials. Specific recommendations are not given by the AHA and ESC[88].

However, it seems more realistic, as suggested by the ACCP[54], that a patient with a large patent foramen ovale and/or interatrial septal aneurysm who has suffered from an unexplained ischemic stroke, or who presents with multiple ischemic although asymptomatic cerebral lesions should be considered for chronic oral anticoagulation (target INR 2.5). This therapeutic approach showed a similar efficacy in preventing recurrent cerebral ischemic events compared to shunt surgical closure, but was superior to antiplatelet drugs[106]. Percutaneous transcatheter closure of patent foramen ovale could be considered a safe and definitive therapeutic approach[107,108] but long-term follow-up studies are still lacking.

In summary, oral anticoagulation (INR 2.0-3.0) is recommended in patients with patent foramen ovale and/or interatrial septal aneurysm with previous stroke, TIA or ischemic, although asymptomatic, cerebral lesions.

Endocarditis

The incidence of native valve infective endocarditis is 1.7-6.2 cases per 100 000 person-years, while in patients with prostheses the frequency is 0.94 per 100 000 patient-years[109]. Cardioembolic stroke occurs in 6-31% of the patients treated, most commonly in the territory of the middle cerebral artery[110]. A thrombus length > 10 mm, mobile vegetations[111], and involvement of the mitral valve are associated with an increased risk of embolization[112]. Oral anticoagulants are not recommended in this condition, as they can induce bleeding without reducing the risk of embolization[113,114]. On the other hand, oral anticoagulants should be continued in patients already treated for specific indications that *per se* imply a high thromboembolic risk (mechanical prosthesis, atrial fibrillation, etc.)[54]; however, if these patients show neurological symptoms, it is more prudent to discontinue anticoagulant therapy and exclude intracranial bleeding[51]. A particular condition is non-bacterial thrombotic endocarditis, which is often secondary to tumors, disseminated intravascular coagulation, sepsis and burns. The rate of thromboembolism may range from 14 to 90%[115] and heparin may be the drug of choice, though there are no published studies to support this therapeutic option. Oral anticoagulants do not seem to be efficacious[54].

In summary, oral anticoagulants are not recommended in bacterial endocarditis. Oral anticoagulants should be continued in patients with bacterial endocarditis and other indications for their use (atrial fibrillation, prosthesis, etc.); the temporary interruption of treatment is indicated when cerebral bleeding, which must be confirmed at computed tomography or magnetic resonance, is suspected. Heparin seems to be the treatment of choice in non-bacterial thrombotic endocarditis.

Aortic plaque

Atherosclerotic plaques in the ascending aorta or in its proximal arch generally represent a risk factor for stroke in subjects > 60 years. This risk is markedly increased in patients with plaques > 4 mm thick (OR 9.1,

95% CI 3.3-25.2)[116], while a mobile component of the plaque increases the risk to 14. Moreover, recurrent ischemic stroke is significantly predicted by the presence of aortic plaques of a thickness ≥ 4 mm[117] (including the aortic wall). On the other hand, smaller plaques were found to be significantly associated with an increased risk for ischemic stroke in women but not in men[118]. It is worth noting that hyperhomocysteinemia may play a crucial role in the progression of the atheroma[119]. From a practical point of view, in agreement with the ACCP[54], warfarin (target INR 2.5) is recommended in patients with a mobile plaque with or without a previous stroke, since at least two studies strongly indicate that coumarins are superior to antiplatelet therapy in primary and secondary prophylaxis[120,121]. However, a recent retrospective study has challenged this assessment indicating that warfarin is not effective in the prevention of major thromboembolic events[122]. The AHA and ESC do not provide recommendations regarding this condition.

In summary, oral anticoagulation (INR 2.0-3.0) is recommended in patients with a mobile aortic atheroma or > 4 mm plaques.

Antiphospholipid syndrome

The antiphospholipid syndrome is an autoimmune disorder that may be found in patients who have suffered from arterial and/or venous thrombosis and recurrent fetal loss[123]. The syndrome may be associated with mild thrombocytopenia. However, the diagnosis of the antiphospholipid syndrome must not only be made on the basis of a clinical event, but it also requires laboratory criteria[124]. The latter include both coagulation and serological determinations. Coagulation tests are aimed at searching for the presence of the lupus anticoagulant. Several tests are required since the autoantibody family of this syndrome is rather large. Diagnosing the presence of the lupus anticoagulant requires a prolonged phospholipid-dependent coagulation time, no correction of the coagulation time on mixing the patient's sample with normal plasma, and correction of the prolonged coagulation time by addition of excess phospholipids[125]. The activated partial thromboplastin time, kaolin clotting time, and the dilute Russell's viper venom test are the most widely used coagulative screening tests for this purpose. Serological evidence of antiphospholipid antibodies is based on the determination of anticardiolipin antibodies and/or anti beta 2 glycoprotein I[126]. A patient can be declared positive both for lupus anticoagulant and/or antiphospholipid antibodies if the abnormalities of these tests are confirmed on two occasions at least 6 weeks apart. A definitive diagnosis of the antiphospholipid syndrome is therefore made if at least either of the clinical events and laboratory criteria are concomitantly present. Among arterial thrombotic events, stroke is present in about 13%[127]. Oral anticoagulants are recommended in patients who have this syndrome and also have a history of cerebral infarction. For years the recommended oral anticoagulation target has been an INR > 3, mainly on the basis of a retrospective investigation[128]. However, several cohort studies indicated that a less aggressive anticoagulation may also be appropriate, thus reducing the risk of bleeding[129-131]. A prospective randomized study on the efficacy of two different target INR (3.0-4.0 vs 2.0-3.0) has terminated and the results are at present being analyzed[132].

In summary, oral anticoagulation (target INR 2.5) is recommended in patients with the antiphospholipid syndrome.

Oral anticoagulant therapy in practice: is it so hard for patients and doctors?

Patients and doctors generally believe that OAT is difficult to manage and that it implies an important risk of both bleeding and re-thrombosis. Though OAT is affected by diet[133], intercurrent disease and the interference of several drugs[134], seasonal variations[135], and the doctor's experience in handling such agents[136], its management has significantly improved in the past few years thanks to the setting up of Anticoagulation Clinics. These were introduced in Italy in 1989 when the Italian Federation for the Surveillance of Anticoagulated Patients was founded. An increasing number of patients can now be followed in Anticoagulation Clinics with dedicated software programs that use an algorithm to integrate the INR with the anticoagulant dosage while proposing the date of the next visit. This method guarantees good quality performance of the anticoagulant treatment even when compared to manual dosing adjustment[137]. However, we believe that an Anticoagulation Clinic should not follow more than 500 patients and that smaller centers should be encouraged in peripheral zones to reduce the patient's discomfort and the pressure caused by the demand. This would allow patients easy access to an Anticoagulation Clinic. These centers could begin their activity using the old manual tilt tube test[138], following predefined criteria for dosing adjustment and thus save on initial costs[139]. Whether they use the computer-assisted method or the manual method, doctors in Anticoagulation Clinics should play a crucial role in patient education[140]. In our experience, the administration of questionnaires aimed at improving the adherence of the patients to the therapy and at knowing how many patients have not yet realized why they are being treated may represent a useful tool for improving the performance in an Anticoagulation Clinic[141]. Doctors should be ready to give precise answers to patients' questions about the risk of bleeding or re-thrombosis entailed by this therapy. On the basis of findings from studies carried out by the Italian Anticoagulation Clinics (ISCOAT)[142], the answers

should be as follows: fatal bleeding (0.25 per 100 patient/years) was reported in 5 out of 153 bleeding episodes (7.6 per 100 patient/years), while the major bleeding episodes were 23 (1.1 per 100 patient/years). The rate of bleeding was higher in patients ≥ 70 years (10.5 per 100 patient/years), the incidence of major bleeding being 2.1 per 100 patient/years[143]. During follow-up (2011 patient/years), 70 thrombotic episodes were reported (3.5 per 100 patient/years), 20 of which were fatal[144]. Warfarin and acenocoumarol were the coumarins used in the ISCOAT study. Despite the fact that the two drugs have different half-lives (36 hours for warfarin and 10 hours for acenocoumarol)[145] and different anticoagulation activities (mean warfarin/acenocoumarol weekly dose ratio 2.08), there was no difference in terms of bleeding episodes[146].

But what about the quality of life of anticoagulated patients? What is their point of view? Is it really hard to have periodical visits and blood samplings? We have tried to answer these questions by means of a study[147] in which we found that only few anticoagulated patients (11%) complained of limitations to their lifestyle. The majority of patients therefore accepted their OAT without being particularly worried, despite the need of periodic clinical and laboratory controls. They also considered the doctor-patient relationship very important and useful in solving other health problems. Elderly patients represent a separate case. Although their risk of bleeding is higher than that of people < 65 years, they generally show a better compliance. Although elderly patients deserve special attention[141], it does not appear that they are more difficult to treat with oral anticoagulants, as stated in a survey dedicated to physician's attitudes and beliefs on this topic[148]. In conclusion, the practice of self-management is now to be considered safe in selected patients[149,150], and could further improve the approach to oral anticoagulation. Whilst awaiting new oral antithrombotic drugs that promise no monitoring and no dietary or pharmacological interference[151], coumarins remain an effective treatment that should not be discouraged so long as it is adequately employed.

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