

# MANAGEMENT OF ANTITHROMBOTIC THERAPY IN PATIENTS WITH STROKE: WHERE DO WE STAND IN 2018?

## MANEJO DA TERAPIA ANTITROMBÓTICA EM PACIENTES COM ACIDENTE VASCULAR CEREBRAL: ONDE ESTAMOS EM 2018?

### ABSTRACT

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Received on 06/21/2018,  
Accepted on 09/17/2018

Stroke is the leading cause of disability worldwide, and is currently also considered the second leading cause of death in Brazil. Ischemic stroke is the most common subtype and can be subdivided etiologically into cardioembolic, atherosclerotic (large artery atherosclerosis or small vessel disease-lacunae), cryptogenic or strokes of other etiologies. Depending on the etiology, secondary prophylaxis of new events should be undertaken with specific antithrombotic medications. Therefore, a thorough investigation of ischemic vascular event etiology is essential for the introduction of appropriate secondary prophylaxis. Antithrombotic therapy after ischemic stroke has evolved considerably in the last decade. The incorporation of direct-acting anticoagulants into clinical practice represents a major advance, particularly for stroke and atrial fibrillation patients, since such medications are safer and more effective for the treatment of high-risk patients. In this article, we will discuss the use of antithrombotics in stroke patients at different post-stroke stages and in the distinct possible etiologies.

**Keywords:** *Thrombolytic Therapy; Stroke; Atrial Fibrillation.*

### RESUMO

O acidente vascular cerebral (AVC) é a maior causa de incapacidade em todo mundo, e atualmente é também considerado como a segunda maior causa de morte no Brasil. O AVC isquêmico é o subtipo mais comum e pode ser subdividido etiologicamente em cardioembólico, aterosclerótico de grandes ou pequenas artérias (lacunas), criptogênico ou de outras etiologias. Dependendo da etiologia encontrada, a profilaxia secundária de novos eventos deve ser feita através de medicações antitrombóticas específicas. Portanto, investigar adequadamente a etiologia do evento vascular isquêmico é fundamental para a instituição da profilaxia secundária apropriada. A terapia antitrombótica pós-AVC isquêmico evoluiu consideravelmente na última década. Especificamente para pacientes com AVC e fibrilação atrial, a incorporação de anticoagulantes de ação direta à prática clínica representa um grande avanço, já que tais medicações são mais eficazes e seguras para o tratamento de pacientes de alto risco. No presente artigo, discutiremos o uso de antitrombóticos em pacientes com AVC em diferentes momentos pós-ícto vascular e nas distintas etiologias possíveis.

**Descritores:** *Terapia Trombolítica; Acidente Vascular Cerebral; Fibrilação Atrial.*

### INTRODUCTION

Stroke is the leading cause of disability worldwide and is currently the second leading cause of death in Brazil.<sup>1,2</sup> Stroke pathophysiology can involve intracranial artery occlusion (ischemic) or rupture of a blood vessel into the encephalic parenchyma or subarachnoid space (hemorrhagic). Ischemic stroke is the most common subtype and can be etiologically subdivided into cardioembolic, atherosclerotic (large-artery atherosclerosis or lacunar small-vessel occlusion), and cryptogenic strokes and strokes of other etiologies (e.g.

arterial dissections, thrombophilia and non-atherosclerotic vasculopathies).<sup>3</sup> Depending on the etiology, secondary prophylaxis to prevent new events should be undertaken with specific antithrombotic medications (Figure 1). The timing of introduction of such medications may vary according to the extent of the ischemic injury and the presence of hemorrhagic transformation in the acute phase.<sup>4</sup> We will discuss the use of antithrombotic agents for the treatment of stroke patients at different post-stroke stages and with different possible etiologies.

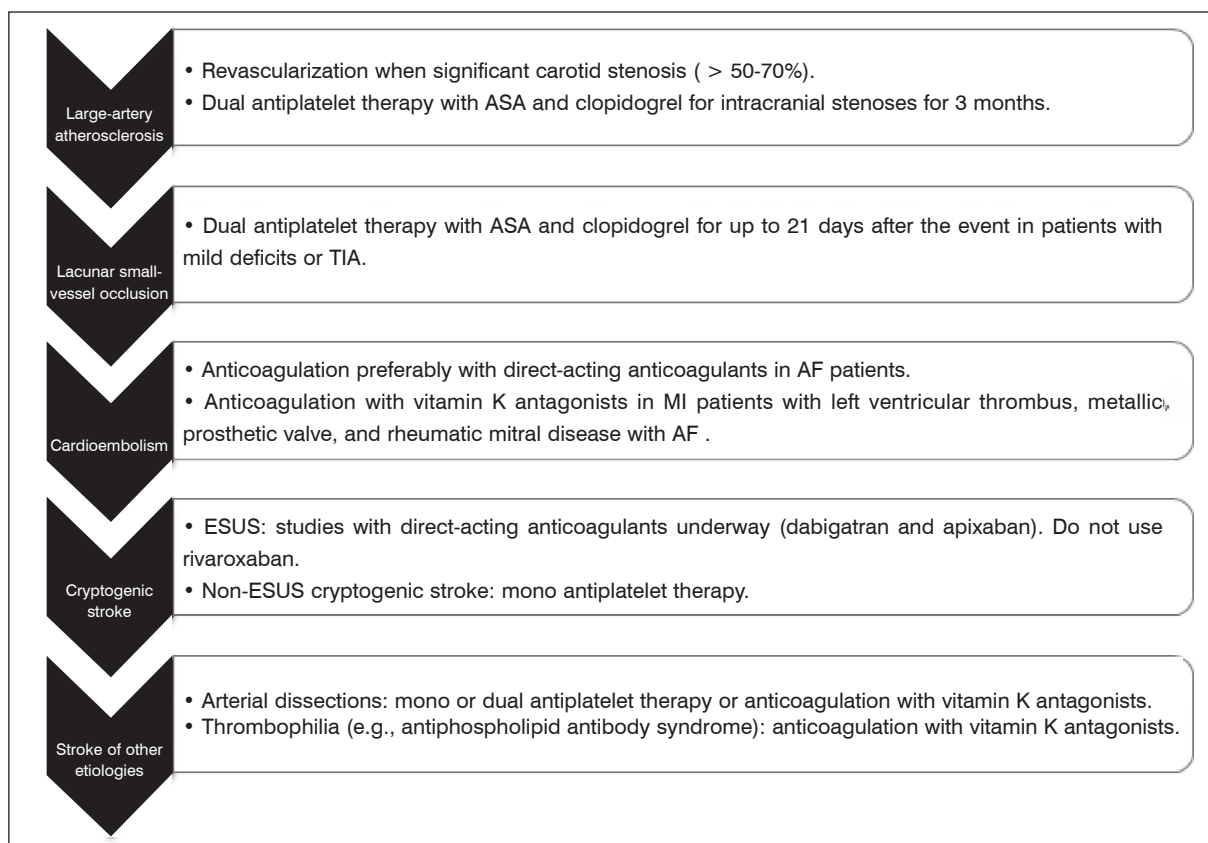


Figure 1. Secondary prophylaxis of ischemic stroke in 2018 according to etiology.

## ANTITHROMBOTIC MEDICATION IN THE ACUTE PHASE OF STROKE

The focus of acute therapy for ischemic stroke patients should be on recanalization of the occluded artery. There is currently strong evidence for treatment with intravenous thrombolytic drugs (rtPA) or mechanical thrombectomy in well-defined therapeutic windows. Some recent studies have suggested that tenecteplase may also be an option for arterial recanalization in acute ischemic stroke.<sup>4</sup> It is essential to introduce an antithrombotic therapy after recanalization and in patients who are not eligible for this type of treatment.

## MONO ANTIPLATELET THERAPY IN THE ACUTE PHASE OF STROKE

Early introduction (within 48 hours) of ASA in large randomized controlled trials (IST and CAST) was beneficial to ischemic stroke patients.<sup>5,6</sup> A meta-analysis including more than 40,000 participants concluded that ASA at doses between 160 and 300 mg/day within 48 hours of an ischemic stroke reduces the risk of recurrence of ischemic events without considerable risk of hemorrhagic complications and is associated with better functional outcomes.<sup>7</sup> To prevent death or disability, the number needed to treat is 79. Administration of ASA is generally postponed for 24 hours in patients treated with intravenous alteplase, but it may be considered earlier when concomitant conditions are present for which ASA treatment is known to be substantially beneficial in the absence of intravenous alteplase or when discontinuation can represent

a significant risk.<sup>4</sup> Rectal or nasogastric administration is indicated for patients with dysphagia.

Limited data have been collected on use of other antiplatelet agents in treatment of acute ischemic stroke. However, in patients with ASA contraindication, administration of other antiplatelet agents should be considered.

The SOCRATES (Acute Stroke or Transient Ischemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes) study was a randomized double-blind placebo-controlled study on ticagrelor versus ASA started within 24 hours in patients with ischemic stroke with mild symptoms (score in the National Institutes of Health Stroke Scale - NIHSS  $\leq 5$ ) or transient ischemic attack (TIA with ABCD2 [Age, Blood Pressure, Clinical Characteristics, Duration, Diabetes] score  $\geq 4$ ). Ticagrelor was not superior to ASA with a primary composite outcome of stroke, myocardial infarction (MI), or death within 90 days. However, as there were no significant safety differences between the two groups, ticagrelor may be a reasonable alternative for treatment of stroke patients for whom ASA is contraindicated.<sup>8</sup> In a prespecified exploratory analysis, ticagrelor was superior to ASA in a subgroup of patients with large-artery stroke of possible atherosclerotic etiology (ipsilateral atherosclerotic stenosis of an extracranial or intracranial artery, including patients with  $<50$  percent stenosis, mobile thrombus, or  $\geq 4$  mm plaque in the aortic arch).<sup>9</sup>

Efficacy of intravenous tirofiban and eptifibatide has not been established in patients with acute ischemic stroke. However, prospective, randomized, open phase II trials evaluating tirofiban and eptifibatide suggested that these drugs were safe for treatment of these patients. Single-arm studies of

eptifibatide as an adjunct therapy to intravenous alteplase have suggested that more data are needed to establish the safety and efficacy of these drugs.<sup>10,11</sup> Administration of other glycoprotein IIb/IIIa receptor antagonists, including abciximab, for the treatment of stroke is potentially harmful and should not be considered. A Cochrane review of intravenous glycoprotein IIb/IIIa receptor antagonists for the treatment of ischemic stroke reported that these agents are associated with a significant risk of intracranial hemorrhage without a measurable decrease in death or disability.<sup>12</sup> Most of these review data apply to abciximab, which was studied in the AbESTT study (Study of Effectiveness and Safety of Abciximab in Patients With Acute Ischemic Stroke). This phase III study was terminated early because of unfavorable results in a risk-benefit analysis.<sup>13</sup>

In summary, administration of ASA is recommended in patients with ischemic stroke within 24 to 48 hours after onset of symptoms.

Clopidogrel is an alternative for ASA-intolerant patients, although the efficacy of this antiplatelet agent for treatment of acute stroke has not been established. On the basis of the SOCRATES study results, ticagrelor may also be a reasonable alternative for stroke patients for whom ASA is contraindicated.<sup>4</sup>

## DUAL OR TRIPLE ANTIPLATELET THERAPY IN THE ACUTE PHASE OF STROKE

The use of dual antiplatelet therapy with ASA and clopidogrel for a short period of time has been effective in patients with TIA or ischemic stroke with minor deficits. The CHANCE trial randomized 5,170 Chinese patients within 24 hours of onset of high-risk TIA or ischemic stroke with minor deficits for dual antiplatelet therapy with clopidogrel and ASA (300 mg loading dose followed by 75 mg daily for 90 days, plus 75 mg of ASA daily for the first 21 days) or placebo. The primary outcome of 90-day stroke recurrence (ischemic or hemorrhagic) favored dual antiplatelet therapy when compared to ASA alone. Long-term follow-up results showed a long-lasting treatment effect, but secondary stroke prevention was only different within the first 90 days. The restricted ethnic population and treatment standards in the CHANCE study limited generalization of results. As such, the combination of clopidogrel and ASA has not been routinely recommended in stroke treatment guidelines.<sup>14</sup> The recently published POINT study showed that patients with lower deficit ischemic stroke or high-risk TIA who received a combination of clopidogrel and ASA (600 mg loading dose followed by 75 mg daily, plus 50 to 325 mg of ASA daily) had a lower risk of major ischemic events but a greater risk of severe hemorrhage at 90 days than did patients who received only ASA.<sup>15</sup>

The TARDIS study, which included more than 3,000 patients with acute ischemic stroke or TIA, compared triple antiplatelet therapy with ASA, clopidogrel, and dipyridamole versus clopidogrel alone or ASA and dipyridamole. Treatment was started within 48 hours after onset and continued for 30 days. The trial was stopped because of the lack of therapeutic efficacy. Triple antiplatelet therapy did not reduce the incidence or severity of recurrent stroke or TIA within 90 days but increased the risk of major hemorrhage.<sup>16</sup>

In summary, 21-day treatment with dual antiplatelet therapy (ASA and clopidogrel) initiated within 24 hours of onset of symptoms should be considered for early secondary prevention of stroke in patients with TIA or ischemic stroke with minor deficits.<sup>4</sup>

## ANTICOAGULATION IN THE ACUTE PHASE OF STROKE

Urgent anticoagulation is not recommended for treatment of acute ischemic stroke patients to prevent early recurrence, avoid progressive worsening, or improve clinical outcomes. Some specialists use early anticoagulation for various ischemic stroke subtypes, including cardioembolic stroke due to atrial fibrillation, large-artery stenosis, or arterial dissections. However, even for these patients, the literature does not support use of anticoagulants in the acute phase. Other subgroups with a particularly high risk of recurrent embolism, such as patients with mechanical heart valves or intracardiac thrombus, were not included or were underrepresented in studies evaluating the use of acute antithrombotic therapy for stroke treatment.<sup>4</sup>

Since publication of their 2013 guideline, the American Stroke Association (ASA) also suggests that there is no benefit of urgent anticoagulation in patients with acute ischemic stroke.<sup>17</sup> Two updated meta-analyses confirmed the lack of benefit of emergency anticoagulation.<sup>18,19</sup> An additional study not included in these meta-analyses investigated the efficacy of low molecular weight heparin (LMWH) compared with ASA for prevention of early neurological deterioration in a randomized controlled non-blinded study. Although there was a statistically significant difference in early neurological deterioration at 10 days post-admission, there was no difference in six-month modified Rankin scale score.<sup>20</sup>

Ideal management of acute ischemic stroke patients with radiological evidence of non-occlusive intraluminal thrombus (e.g. in the cervical carotid artery or vertebrobasilar system) remains uncertain. Some small observational studies suggested that short-duration intravenous heparin or LMWH may be safe, but further studies are necessary to appropriately establish safety and efficacy.<sup>21,22</sup>

Observational studies suggest the safety and viability of ischemic stroke treatment using thrombin inhibitors alone or as an adjunct therapy to alteplase. Dabigatran is a direct thrombin inhibitor that was studied in 53 patients with mild TIA or stroke (NIHSS  $\leq 3$ ) without occurrence of asymptomatic intracranial hemorrhage at 30 days.<sup>23</sup> ARTSS (Argatroban With Recombinant Tissue Plasminogen Activator for Acute Stroke) was a pilot open-label safety study of argatroban plus alteplase intravenous infusion in 65 patients with complete or partial occlusive thrombus diagnosed by transcranial Doppler.<sup>24</sup> In the ARTSS-2 phase II study, patients with acute ischemic stroke treated with alteplase ( $n = 90$ ) were randomized to receive placebo or argatroban (100  $\mu\text{g/kg}$  bolus, followed by infusion at 1 or 3  $\mu\text{g/kg}$  per minute for 48 h). Rates of intracranial hemorrhage were similar among the control, low dose, and high dose arms (10%, 13%, and 7%, respectively).<sup>25</sup> Efficacy of argatroban, dabigatran, and other thrombin inhibitors for stroke treatment is not well established and more clinical studies are needed.<sup>4</sup>

Data on the use of Xa factor inhibitors (rivaroxaban, apixaban, edoxaban) for acute treatment of ischemic stroke patients

are still limited. Many prospective observational studies are in progress.<sup>4</sup> A randomized clinical trial of 195 patients with mild acute ischemic stroke (acute ischemic stroke smaller than one third of the territory of the middle cerebral artery, half of the territory of the anterior cerebral artery, half of the territory of the posterior cerebral artery, or half of a cerebellar hemisphere) and atrial fibrillation showed new ischemic lesions or new intracranial hemorrhage as visualized by magnetic resonance imaging after four weeks in 49.5% of the patients who received rivaroxaban and 54.5% of the patients who received warfarin, a non-significant difference. Each group had one ischemic stroke recurrence and there were no symptomatic intracranial hemorrhages. The authors concluded that rivaroxaban and warfarin showed comparable safety and efficacy in patients with acute ischemic stroke related to AF.<sup>26</sup>

In selected cases where anticoagulation is indicated for treatment of an acute stroke, a neuroimaging study should always be performed to exclude hemorrhage and to estimate infarct size. Early anticoagulation should always be avoided in the case of a large-volume infarct or uncontrolled hypertension. Although there is no standard definition, many stroke specialists consider “large infarcts” to involve more than one third of the territory of the middle cerebral artery or more than half of the territory of the posterior cerebral artery. Infarct size can also be clinically estimated, but this process may underestimate the actual volume of infarct when the so-called “silent” areas of the association cortex are involved. Clinical estimates of infarct size can be improved by using validated scales correlated with volume and clinical outcome, such as the NIHSS. In general, patients with an NIHSS score > 15 have large-volume infarcts as determined by neuroimaging. Infarcts in strategic areas such as the cerebellum and

brainstem are usually small in volume but may preclude the use of anticoagulants as hemorrhage in strategic areas can lead to serious clinical consequences.<sup>27</sup>

In summary, use of full-dose parenteral anticoagulation is not recommended for treatment of non-selected acute ischemic stroke patients, as previous studies have shown limited efficacy and increased risk of hemorrhagic complications.<sup>4</sup>

SECONDARY PROPHYLAXIS

After the acute phase of an ischemic stroke, it is extremely important to define the etiology of the ischemic event to properly implement secondary prophylaxis. Tables 1–3 show a variety of useful etiological classifications to evaluate stroke patients.<sup>20, 28, 29</sup>

ANTIPLATELET THERAPY  
IN NONCARDIOEMBOLIC  
ISCHEMIC STROKE

In 2016, a pooled analysis of more than 15,000 patients from 12 studies evaluating ASA as a secondary prevention strategy for ischemic stroke showed that ASA reduced the relative risk of recurrent ischemic stroke in the first six weeks by 58%. The benefit of ASA was greatest for patients with TIA or stroke with minor deficits. ASA doses in stroke prevention studies ranged from 20 to 1,300 mg. Most studies suggested that 50 to 325 mg/day of ASA is as effective as higher doses.<sup>30</sup> A review of 195 secondary prevention studies showed that doses of 75 to 150 mg/day resulted in the same risk reduction compared with placebo as doses of 150 to 325 mg/day.<sup>31</sup>

Table 1. TOAST classification.

<b>1 – Large-artery atherosclerosis</b>	Artery evaluation (through carotid Doppler, transcranial Doppler, magnetic resonance angiography, or angiography of cranial vessels) shows stenosis greater than 50% or occlusion of large arterial branches (intra- or extracranial) on the same side of the central lesion, or complex plaque in the ascending or transverse aorta (> 4mm). Cranial tomography (CT) or skull MRI usually show brain lesions larger than 1.5 cm in diameter. Other tests should exclude potential sources of cardioembolism.
<b>2 - Cardioembolism</b>	Cardioembolic infarctions originate from cerebral vessel occlusions by cardiac emboli. The main potentially embolic cardiac diseases can be classified as high and medium risk of embolization (Table 3).
<b>3 – Lacunar small-vessel occlusion</b>	Infarcts caused by occlusion of small cerebral vessels are also called lacunar infarcts. The patient presents lacunar syndrome (neurological deficit without cortical impairment) and, in general, CT or MRI show small lesions (lacunae) in the territory of perforating arteries, i.e., nuclei of the base, thalamus, brainstem, radiating crown, and internal and external capsules, smaller than 1.5 cm in diameter. These lesions occur due to degeneration of small vessels and perforating arterioles by direct action of chronic arterial hypertension, with or without diabetes mellitus.
<b>4 – Strokes of other etiologies</b>	Strokes of other etiologies include all causes that are different from classifications 1-3 in this table. Examples include non-atherosclerotic vasculopathies (Moyamoya, arterial dissection), hematological disorders (sickle cell anemia), coagulopathies (fibrinolytic factor deficiency), and vasculitis (varicella infection, lupus, meningitis).
<b>5 - Strokes of undetermined etiology</b>	Strokes of undetermined etiology are not included in the previous categories despite complete investigation, or have more than one etiology.

Table 2. CCS-TOAST classification (causative classification system).

Ischemic stroke mechanism	Confidence level	Criteria
Large-artery atherosclerosis	Evident	1. Diameter reduction by 50% or occlusive/stenotic vascular disease caused by atherosclerosis in a clinically relevant intracranial artery, and 2. Absence of acute infarction in vascular territories other than in the territory of the obstructed or stenotic artery.
	Probable	1. Previous history of one or more transient monocular blindness (TMB), TIA, or ischemic stroke in the territory of the index artery affected by atherosclerosis in the last month, or 2. Evidence of proximal occlusive stenosis or complete nonchronic occlusion judged to be due to extracranial or intracranial atherosclerosis in a clinically relevant artery (except for the vertebral arteries), or 3. Presence of ipsilateral, unilateral, or multiple watershed infarct territories, temporally separated and exclusively in the affected artery territory.
	Possible	1. Presence of an atherosclerotic plaque protruding into the lumen and causing stenosis (50%) in a clinically relevant extracranial or intracranial artery, and history of two or more TMBs, TIAs, or ischemic strokes in the territory of the index artery affected by atherosclerosis, at least one event in the previous month, or 2. Evident large-artery atherosclerosis in the absence of a complete diagnostic investigation for other mechanisms.
Cardio-aortic embolism	Evident	Presence of a high-risk cardiac source for cerebral embolism.
	Probable	1. Evidence of systemic embolism, or 2. Presence of multiple acute infarcts closely related in time in either the right or left hemisphere, or in both anterior and posterior circulations, in the absence of occlusion or proximal occlusive stenosis of all related vessels, and of other diseases that can cause multifocal ischemic cerebral injury (vasculitis). Vasculopathies and hemostatic or hemodynamic changes should not be present.
	Possible	1. Presence of a cardiac condition with low or uncertain risk of cerebral embolism, or 2. Evident cardio-aortic embolism in the absence of a complete diagnostic investigation for other mechanisms.
Occlusion of small arteries	Evident	Imaging shows a single clinically relevant acute infarct less than 20 mm in diameter in the territory of the nuclei of the base or the brainstem, perforating arteries in the absence of any other pathology in the original artery, and in the place of origin of the perforating artery (focal atheroma, vessel dissection, vasculitis, vasospasm, etc.).
	Probable	Presence of stereotyped lacunar TIAs in the previous week.
	Possible	1. Presence of a classic lacunar syndrome in the absence of images sensitive enough to detect small infarcts, or 2. Evident small artery occlusion in the absence of a complete diagnostic investigation for other mechanisms.
Other causes	Evident	Presence of a specific disease involving clinically relevant cerebral arteries.
	Probable	A process of the specific disease that occurred in clear temporal relationship and near the onset of cerebral infarction, such as arterial dissection, cardiac or artery surgery, and cardiovascular interventions.
	Possible	Evidence of another cause in the absence of a complete investigation of the mechanisms listed above.
Undetermined causes	Unknown (with no obvious or possible causes for the previously mentioned mechanisms)	Cryptogenic embolism.
		1. Angiographic evidence of abrupt blood flow interruption in angiographically normal vessels in intracranial arteries, or 2. Imaging showing complete recanalization of a previously occluded artery, or 3. Presence of multiple closely related acute infarcts with no detectable abnormality in relevant vessels.  Other cryptogenic strokes: those that do not meet the criteria for cryptogenic embolism or have incomplete evaluation: absence of diagnostic tests which, based on the judgment of the examiner, would have been essential to diagnose the underlying cause.
	Not classified	The presence of more than one apparent mechanism or no probable evidence to establish a single cause.



Table 03. High and medium risk sources for cardioembolism according to the TOAST classification.

High-risk sources	Medium-risk sources
Synthetic valve prosthesis	Mitral valve prolapse
Mitral stenosis with atrial fibrillation	Mitral annular calcification
Atrial fibrillation (not isolated)	Mitral stenosis without atrial fibrillation
Sessile left atrial thrombus	Left atrial turbulence
Sinus node disease	Atrial septal aneurysm
Acute myocardial infarction (< 4 weeks)	Patent foramen ovale Atrial flutter
Left ventricular thrombus	Isolated atrial fibrillation
Dilated cardiomyopathy	Biological valve prosthesis
Akinetic left ventricular segment	Aseptic endocarditis
Atrial myxoma	Congestive heart failure
Infective endocarditis	Hypokinetic segment of the left ventricle
	Acute myocardial infarction within the last 4 weeks to 6 months

The CAPRIE study randomized more than 19,000 patients with recent stroke, MI, or symptomatic peripheral artery disease for treatment with ASA (325 mg) or clopidogrel (75 mg). The primary outcome (composite outcome of stroke, MI, or vascular death) was significantly reduced with clopidogrel treatment compared with ASA. However, the benefit of clopidogrel compared to ASA in the CAPRIE study varied according to disease etiology. The greatest benefit was observed in patients with peripheral artery disease, and the difference in composite outcome between treatment with clopidogrel and ASA in patients with recent stroke was not significant.<sup>32</sup>

Randomized clinical trials, such as WARSS (Warfarin Aspirin Recurrent Stroke Study) and WASID (Warfarin Aspirin Symptomatic Intracranial Disease) found no difference in benefit between antiplatelet therapy and anticoagulant therapy with regard to reduced risk of ischemic stroke. However, risk of severe hemorrhage and death was greater with warfarin.<sup>33, 34</sup> The SAMMPRIS study (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis) showed that an aggressive medical treatment (including dual antiplatelet therapy, statin, and antihypertensives, as well as sedentary lifestyle and obesity management) was more effective than the use of stents for patients with recently symptomatic high-grade (above 50%) intracranial artery stenosis.<sup>35</sup>

For most ischemic stroke patients, combined long-term use of ASA and clopidogrel offers no additional benefit in prevention of recurrence than using either agent alone, but it substantially increases the risk of hemorrhagic complications. This conclusion is based on results from the MATCH study with more than 7,000 ischemic stroke or TIA patients with previous history of MI, stroke (in addition to the index event),

diabetes, angina, or symptomatic peripheral artery disease. The primary outcome was a composite of ischemic stroke, MI, and acute ischemia readmission. The patients were randomly assigned to wither a combination of clopidogrel (75 mg/day) and ASA (75 mg/day) or to clopidogrel (75 mg/day) alone. Dual antiplatelet therapy did not reduce risk of major vascular events compared to clopidogrel alone and was associated with a significant increase in hemorrhagic complications (intracranial and gastrointestinal hemorrhage).

The effects of the combination of ASA plus dipyridamole for prevention of secondary ischemic stroke seem additive. According to the ESPS2 and ESPRIT studies, the combination of extended-release dipyridamole and ASA is significantly more effective than ASA alone for stroke prevention.<sup>37, 38</sup> In the ESPS2 study, stroke rate at 24 month follow-up was significantly lower in the prolonged-release dipyridamole group compared to the ASA alone group. In the ESPRIT study, at an average follow-up of 3.5 years, the composite primary outcome (death from all vascular causes, nonfatal stroke, nonfatal MI, or major hemorrhagic complication) was significantly less frequent in the ASA plus dipyridamole group than in the ASA group.

In summary, ASA, clopidogrel, and the combination of extended-release dipyridamole with ASA (not available in Brazil) are acceptable options as secondary prophylaxis strategies for noncardioembolic ischemic stroke.

## ANTICOAGULATION IN PATIENTS WITH CARDIOEMBOLIC STROKE

Approximately 10% of the patients with acute ischemic stroke or TIA have AF detected during hospitalization, whereas an additional 11% may exhibit AF if they undergo continuous electrocardiographic monitoring for 30 days.<sup>39</sup>

Many clinical trials demonstrated the therapeutic effect of warfarin compared to placebo to prevent thromboembolic events in patients with nonvalvular AF. A pooled data analysis of five primary prevention studies showed a relative risk reduction of 68% and an absolute reduction in annual stroke rate from 4.5% to 1.4% in patients allocated to the dose-adjusted warfarin group.<sup>40</sup>

The optimal intensity of oral anticoagulation for stroke prevention in AF patients must maintain INR between 2.0 and 3.0. Results of a large case-control and a randomized controlled study suggested that the efficacy of oral anticoagulation decreases significantly with INR below 2.0.<sup>41</sup> Unfortunately, a high percentage of AF patients have subtherapeutic levels of anticoagulation and therefore are inadequately protected from stroke. AHA/ACC/HRS guidelines recommend warfarin, dabigatran, rivaroxaban, or apixaban for patients with non-valvular AF and prior stroke or TIA.<sup>42, 43</sup>

Dabigatran was compared with dose-adjusted warfarin in a study (RE-LY) involving more than 18,000 AF patients that excluded patients with a prior history of stroke in the previous 14 days. Dabigatran was superior to warfarin at a dose of 150 mg twice per day and not significantly inferior at a dose of 110 mg twice per day for prevention of stroke or systemic embolism, including the subset of participants who had experienced a previous stroke.<sup>44</sup> Rivaroxaban was compared with dose-adjusted warfarin in the ROCKET AF study, which included more than 14,000 patients and was considered not inferior (1.7 versus

2.2% per year, respectively) for the primary composite outcome of stroke or central nervous system systemic embolism. Similar to that in the entire cohort, no significant differences were observed in the primary composite outcome between rivaroxaban and warfarin in the subgroup of patients (52%) with previous stroke. The ROCKET AF study also excluded patients who had a stroke in the previous 14 days.<sup>45</sup> Apixaban was compared with adjusted-dose warfarin in the ARISTOTLE study, which involved more than 18,000 patients, and was superior to warfarin for prevention of stroke or systemic embolism, resulting in a lower overall mortality rate (3.5 versus 3.9%). Of the 3,436 patients with prior stroke or TIA, there was no significant difference in stroke and systemic embolism between apixaban and warfarin (apixaban at 2.5% versus warfarin at 3.2%). The ARISTOTLE study excluded patients with a history of stroke within the previous seven days.<sup>46</sup>

Edoxaban was compared with warfarin in a study of more than 21,000 patients. Edoxaban was not inferior in the primary outcome of efficacy and caused less hemorrhage. Results were similar in the subgroup of patients with previous stroke or TIA. The ENGAGE TIMI 48 study excluded patients with prior stroke in the previous 28 days.<sup>47</sup>

Anticoagulation with warfarin is also indicated for patients with stroke or MI with left ventricular thrombus, prosthetic metal valve, and rheumatic mitral disease with AF.<sup>42</sup>

In summary, according to the results of the studies discussed in this review, European AF and AHA/ASA guidelines recommend use of direct-acting anticoagulants as opposed to warfarin for secondary prophylaxis of stroke in AF patients. The correct time to start these medications after an ischemic stroke is controversial and has not been systematically studied. Based on opinions of specialists, it is reasonable to start direct-acting anticoagulants for TIA and AF patients 24 hours after the onset of symptoms and continue for three days for patients with mild deficits, for six to eight days for patients with moderate deficits once neuroimaging evaluation excludes hemorrhagic transformation, and for twelve to fourteen days for patients with severe deficits once neuroimaging evaluation has excluded hemorrhage.

For stroke and AF patients who already use oral anticoagulation, it is important to investigate adherence to medications and other concomitant etiologies. For example, etiology of the ischemic event in an AF patient could be a severe carotid stenosis that should be revascularized. Treatment of the carotid lesion is the most important intervention, with changing the anticoagulant being less important. Combination of

anticoagulants and antiplatelet agents will rarely be necessary for secondary prevention of stroke. These cases should be cautiously evaluated because of increased risk of hemorrhage caused by combination of antithrombotic drugs. When this combination is necessary (e.g., for AF patients treated with coronary stents in the last 6-12 months), treatment duration should be as short as possible.

## EMBOLIC STROKE OF UNDETERMINED SOURCE (ESUS)

Cryptogenic ischemic strokes (of undetermined source) comprise approximately 25% of all strokes. Advances in imaging techniques and better understanding of stroke pathophysiology have led to reevaluation of cryptogenic stroke. There is strong evidence that most cryptogenic strokes are thromboembolic. Therefore, ESUS was defined in the literature as such: non-lacunar cerebral infarction without proximal artery stenosis or cardioembolic sources, with a clear indication for anticoagulation.<sup>48</sup> As emboli mainly consist of thrombi, anticoagulants are probably more efficient than antiplatelet agents in reducing recurrent cerebral ischemia. Unfortunately, the first study that evaluated use of direct anticoagulants (rivaroxaban) versus ASA showed no benefit of the medication and increased risk of major hemorrhage.<sup>49</sup> Other studies evaluating apixaban and dabigatran in ESUS patients are underway.

## CONCLUSIONS

Antithrombotic therapy after ischemic stroke has evolved considerably in the last decade. Use of direct-acting anticoagulants into clinical practice represents a major advance, particularly for stroke and atrial fibrillation patients, as these medications are safer and more effective for treatment of high-risk patients. A thorough investigation of ischemic vascular event etiology is essential for implementation of appropriate secondary prophylaxis. Secondary prevention of stroke should not be restricted to antithrombotic management. Aggressive management of other vascular risk factors such as dyslipidemia, diabetes, arterial hypertension, and sedentary lifestyle is essential.

## CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

**AUTHORS' CONTRIBUTIONS:** GSS e RDL: realizaram a pesquisa bibliográfica, a revisão do manuscrito e contribuíram com o conceito intelectual do estudo.

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