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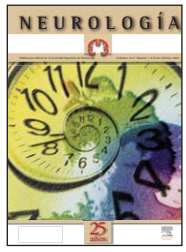

EDITORIAL

Advances in the Prevention of Cerebral Ischaemia Due to Atrial Fibrillation

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Abstract
Introduction: Stroke and atrial fibrillation (AF) are a real vascular epidemic, and the consequences are disastrous. The most common complication of AF is stroke.
Background: The correct aetiological diagnosis of stroke is essential for adequate prevention. The percentage of cryptogenic ischaemic strokes is far too high and the detection of AF needs to be improved. Cardio-embolic cerebral ischaemia due to AF is preventable, however due to medical inertia, the lack of compliance by the patient, and the problems with oral vitamin K antagonist anticoagulants, means that many patients with AF are at risk of suffering from a stroke.
Conclusions: The significant recent advances with drugs such as dronedarone and dabigatran, provide real hope for an improvement in its prevention, and for this reason neurologists must know about them.

PALABRAS CLAVE
Ictus;
Fibrilación auricular;
Prevención;
Dronedarona;
Dabigatrán

Avances en la prevención de la isquemia cerebral por fibrilación auricular

Resumen
Introducción: El ictus y la fibrilación auricular (FA) son una verdadera epidemia vascular, y sus consecuencias son catastróficas. La complicación más común y devastadora de la FA es el ictus.
Desarrollo: El diagnóstico etiológico correcto del ictus es esencial para poder realizar una prevención adecuada. El porcentaje de ictus isquémicos criptogénicos es demasiado elevado, y es preciso mejorar la detección de la FA. La isquemia cerebral cardioembólica por FA es prevenible, pero la inercia médica, la falta de adherencia del paciente y los problemas de los anticoagulantes orales antagonistas de la vitamina K hacen que muchos pacientes con FA estén en riesgo de sufrir una isquemia cerebral.
Conclusiones: Los relevantes avances recientes con fármacos como la dronedarona y el dabigatrán abren una esperanza real para mejorar su prevención y pronto se reflejarán en las guías terapéuticas de prevención y, por lo tanto, los neurólogos debemos conocerlos.

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Vascular diseases constitute a veritable epidemic. Among these, stroke and atrial fibrillation (AF) are of great importance due to their human and social consequences. Both are preventable and treatable, and we should be grateful for the significant progress made during the last year in relation to the prevention of cardioembolic stroke due to AF.

Stroke remains the second leading cause of death in Spain, following cardiovascular disease, and the leading cause in women, according to 2007 data, with a total of 33,034 deaths.[1]

But perhaps the worst part is the number of patients who become dependent or demented after a stroke. Stroke is by far the leading cause of neurological hospitalisation and one of the main consumers of health care costs (4%),[2] both during the acute phase and afterwards. It is the leading cause of disability in adults (up to 53% of patients are left with varying degrees of dependency) and the second leading cause of dementia (30%-50% of patients present cognitive impairment).[3]

More than 117,000 patients were admitted in 2008 into Spanish public hospitals due to a stroke or transient ischemic attack (TIA) as principal diagnosis on discharge.[4]

Atrial fibrillation constitutes a true global epidemic. It is estimated that in Western Europe there are 4.5 million patients with AF, and that this figure could triple or quadruple for 2050.[5] The estimated prevalence is of 3.8% in the population over 60 years and 9% in those older than 80 years.[6] People older than 40 have a 25% (1/4) risk of suffering AF during the course of their lives.[7]

The Aetiology of Stroke: Importance of AF

After arterial hypertension (AHT), AF is the most important causal risk factor (RF), which represents 2/3 of first strokes, together with diabetes mellitus, physical inactivity and smoking.[8] It is the leading causal disease of cardioembolic stroke; the risk of stroke is independent of the baseline AF type (*de novo*, paroxysmal, persistent, permanent) or flutter.[9]

AF increases the risk of stroke by 4 to 5 times.[10] The average annual rate of ischemic stroke in patients with non-valvular AF is 5%, that is, 2 to 7 times higher than those who do not suffer it; this rate increases to over 23% in patients older than 80 years.[10]

It is an independent RF from ischemic stroke, with increased severity, increased recurrence and mortality, and greater dependency.[11-13] Following a cardioembolic stroke, mortality at 2 years is 45%[14] and 80% at 5 years, with a risk of recurrent stroke of 32%.[15]

Stroke associated with AF has a risk of dependency (bed-confinement) 2.2 times higher than for other factors,[16] and the risk of stroke persists even when the AF is asymptomatic.[17] Consequently, the most common and devastating complication of AF is stroke.

It is estimated that AF is responsible for 20% of all ischemic strokes.[18] The problem is that this figure is most likely an underestimation, because the aetiology of stroke (atherothrombotic, cardioembolic, small vessel stroke) is not properly investigated. The Spanish study DIAPRESIC[19] showed that 46% of patients with cerebral infarction did not have an aetiological diagnosis; only 25% underwent a transthoracic echocardiography study and only 4% a Holter study. Therefore, the various series report at least 30% of cryptogenic strokes[9] due to incomplete studies.[19]

A cardioembolic origin of cerebral ischemia may be suspected when it has a sudden clinical onset with maximum deficit from the start, when deficits have a cortical location (hemianopsia, neglect, aphasia) and in some cases, there is a decrease of consciousness or symptoms return very quickly. Neuroimaging (CT/MRI) is suspicious when several areas are affected simultaneously or sequentially, or when there is no haemorrhagic transformation. Neurosonology or cerebral angiography is suspicious when there is a mobile carotid thrombus, early recanalisation of an occluded intracranial vessel or when microemboli are observed in both middle cerebral arteries.[20]

However, suspicion is not sufficient and a cardioembolic source needs to be demonstrated, since the safety of oral anticoagulation therapy (clearly superior to antiplatelet therapy) carries the risk of haemorrhage and guidelines require a defined cardioembolic source.[21]

A thorough investigation of potential embolic sources with echocardiography and arrhythmia detection increases the percentage of patients with stroke caused by AF. For example, 24 h Holter monitoring can detect *de novo* AF in 9.4% of stroke patients.[22] Mobile telemetry (21 days) detects spells of asymptomatic AF in 23% of patients with cerebral stroke or cryptogenic TIA.[23] A study analysing the detection of AF and *de novo* atrial flutter shows different percentages (2.5% to 7.7%), because the studies analysed were not uniform, had different monitoring start times after stroke and used different types of monitoring and different definitions of AF.[24]

Of about 117,000 patients admitted in 2008 to Spanish public hospitals due to stroke or TIA,[4] about 35,000 were due to recurrent stroke or TIA, extrapolating from the incidence of the IBERICTUS[25] study.

The causes of recurrent stroke are medical inertia, patient adherence (compliance and persistence), leading to inadequate control of changing lifestyles and vascular risk factors, indication or failure of antithrombotic treatment, and incorrect aetiological diagnosis.

The etiological diagnosis is essential for correct secondary prevention; otherwise, it may cause recurrences.[21]

Strategies in the Treatment of Auricular Fibrillation and Stroke

The basic treatment scheme for AF is the prevention of heart embolism through antithrombotic therapy and symptomatic treatment through the control of rate and rhythm.[26]

The treatment of choice to reduce cardioembolic risk in the prevention of stroke or TIA associated with AF is oral anticoagulation (OAC), because it shows a significant benefit

over aspirin and the number of patients needed to treat (NNT) to prevent one stroke per year -13 for OAC and 50 for aspirin[27,28]-; if OAC is contraindicated, aspirin should be the treatment, as indicated by current therapeutic guidelines.[21,29-31] A possible alternative would be triflusal combined with low anticoagulation doses.[32]

Symptomatic treatment of AF through rate control (pharmacological, ablation or pacemaker) and/or rhythm control (pharmacological, ablation, pacemaker, defibrillators or surgery) improves tolerance to exercise, quality of life and other symptoms associated with AF and ventricular function. It also reduces sudden death or death caused by heart condition.[26]

However, so far, studies comparing rhythm control and rate control have not shown differences with regard to cardioembolic risk, including stroke, mortality or haemorrhage. Surprisingly, there is a greater tendency towards thromboembolism with rate control therapy, possibly due to temporary control and to withdrawal of anticoagulant therapy.[33]

The AFFIRM[34] and AF-CHF[35] studies demonstrated that AF prevention is not necessarily beneficial: the reduction of AF did not reduce mortality or stroke. In the AFFIRM[34] study, the risk of ischemic stroke was related to the absence of anticoagulation or anticoagulation at suboptimal doses. Something more than simply reducing AF recurrence is necessary.

Problems of Oral Anticoagulation (Vitamin K Antagonists)

Although clearly effective, vitamin K antagonists (dicoumarins and warfarin) have important problems that become evident in clinical practice, leading to under-usage or use in therapeutic doses that are inadequate due to a slow start in their action and metabolization, a narrow therapeutic window, wide variation of metabolism with numerous food and drug interactions, common genetic polymorphisms that affect the dose requirement, the need to monitor coagulation in a regular manner and with frequent dose adjustments, with an added cost. Consequently, medical inertia (indication) and patient adherence (compliance and persistence) are poor. These, together with a subtherapeutic international normalised ratio (INR), leads to inadequate prevention with new or recurrent strokes, and the high INR interval increases the risk of haemorrhage and fear in indicating OAC.

The risk of haemorrhage is another serious problem of OAC, especially the risk of cerebral haemorrhage. This can be minimised by knowing the predictors of cerebral haemorrhage in the treatment of arterial hypertension, and especially the OAC intensity.[36] If a proper OAC is achieved (INR between 2 and 3), the risk of cerebral haemorrhage is acceptable, with a risk of 0.5% per annum and an NNT=200, especially when compared with NNT=13 to avoid 1 stroke per year.[37]

However, the difficulty in maintaining the INR interval, the accessibility of monitoring, the variability of the laboratories and the perceived risk of bleeding (especially in the elderly) all lead to an underutilisation of existing OAC.

Examples of this in everyday practice show that only 15% of patients have an adequate INR[38] and, worse still, up to 73% of patients with AF do not receive adequate antithrombotic therapy in an unjustified manner.[39]

A Canadian investigation in which all patients were ideal candidates for OAC due to non-valvular AF (NVAF) showed that 60% of patients admitted for a first ischemic stroke were not anticoagulated and, of those who did receive the therapy, 75% had a low INR (subtherapeutic). Of the patients with TIA/ischemic stroke, 40% were not receiving OAC, and from those who were, 70% received subtherapeutic doses.[40] There is also evidence pointing to a great variability in INR between countries and centres.[41] The evidence available indicates that the lack of adherence to secondary prevention of the prescribed medication after stroke is a major problem. In a Swedish group, the use of warfarin decreased by 50% 2 years after the stroke[42] and was suspended after 1 year in a much higher rate in patients over 80 years than in those who were younger.[43]

Another myth consists of not using OAC in the elderly with AF. It is precisely at that age that the risk of stroke is higher,[44-46] and studies such as the BAFTA have shown that OAC is superior to aspirin, with a similar risk of haemorrhage, in elderly patients with prior stroke or TIA and a mean age of 82 years.[47]

These data and those from similar studies[48-50] reflect a very serious situation with serious consequences; thus requiring alternatives with a new, ideal OAC that has similar or greater effectiveness, with similar or higher security, with a fixed dose that does not require monitoring, little interaction with foods and drugs, quick start of action and rapid and reversible metabolization and that is cost-effective. We have spent too many years using inadequate prevention in cardioembolic stroke.

Novelties in Treatment Strategies for AF and Stroke Prevention

The antiarrhythmic drug dronedarone controls the rhythm and is free from risk of organ toxicity. In addition, it has recently shown a proven impact on morbidity and mortality, with a significant risk reduction in the primary objective (first hospitalisation for vascular event or death) of 24%.[51] The most surprising finding was a subsequent analysis that showed that dronedarone significantly reduced the annual stroke rate (1.19% compared to 1.79%, hazard ratio [HR]=0.66; 95% CI, 0.46-0.94; *P*=.027), and of other combined vascular events. This difference existed despite the same proportion of drug use in both groups: beta blockers, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists (ARA-II), digoxin, statins and oral anticoagulants or antiplatelet drugs (92%).[52]

Dronedarone is the first antiarrhythmic drug that reduces stroke, so it is a novelty in the management of cardioembolic stroke due to AF. This drug opens up a different therapeutic

avenue in the prevention of cardioembolic stroke, accounting for a greater benefit than the prevention obtained with antithrombotic drugs, probably due to better control of rhythm. Consequently, the neurologist must not only know the data, but should also learn and apply their management when indicated.

There is increasing evidence, as illustrated by several clinical studies, that the use of statins may prevent AF and its recurrences;[53,54] and the blocking of the renin-angiotensin system has also shown a reduced risk of *de novo* AF in studies with ACE or ARA-II inhibitors.[55-57] These drugs, which are already in use in the prevention of ischemic stroke, may therefore have an added benefit in preventing the occurrence of AF or its recurrence.

In most patients (90%) with NVAF, thrombi are located in the atrial appendage.[58] A possible approach to the problem is thus the exclusion of the appendage. The PROTECT AF[59] study (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) shows that the percutaneous implantation of a device occluding the appendage is feasible and can reduce the risk of stroke. This non-inferiority study compared, in 707 patients with AF, the WATCHMAN device implantation (n=463) vs adjusted doses (INR 2-3) of warfarin (n=244). The device was successfully implanted in 88% of cases, and most were taken off warfarin 45 days later. The primary outcome (combination of stroke, unexplained or vascular death and systemic embolism) was similar in both groups. The annual rate of ischemic stroke was low (1.6%), possibly due to low risk (most with a score of 1 or 2 on the CHADS2 risk scale).

Haemorrhagic complications or those related to the procedure were more frequent in the device group. The most common was cardiac effusion in 22 patients (5%), requiring pericardiocentesis or surgery.

The results of the study are promising, but it did not include patients at high risk of stroke, for whom it may have had a higher benefit. Although it could be an alternative in patients with absolute contraindications to OAC, new studies are required.

The ACTIVE A study has recently taken an important step for patients with contraindication to OAC. The combination of aspirin and clopidogrel has shown a clear benefit over aspirin alone in the reduction of severe vascular events, particularly stroke, with an NNT=200 to avoid a fatal or disabling stroke at 1 year; however, there is an increased haemorrhage risk, NNT=500 added for intracranial haemorrhage in 1 year.[60] The combination of aspirin plus clopidogrel shows a clear net benefit compared to aspirin and would be indicated in patients with absolute contraindication for OAC.

The most important novelty is the RE-LY[61] (Randomized Evaluation of Long-Term Anticoagulation Therapy) study, which could represent the ideal OAC so eagerly expected. This is a direct thrombin inhibitor at fixed doses, which does not require monitoring (hence, it is easy to administer) and has few interactions (P-glycoprotein inhibitors such as amiodarone) or major side effects such as hepatotoxicity.

This was a randomized, blind, non-inferiority study, including 18,113 patients with AF (mean age, 71 years) and at least another RF for cerebral stroke, such as prior cerebral stroke or TIA, left ventricular ejection fraction (LVEF)<40%, New York Heart Association (NYHA) Class II-IV heart failure in the previous 6 months and age >75 years or between 65 and 74 years with diabetes mellitus, arterial hypertension or coronary disease. It compared fixed doses of dabigatran etexilate (a prodrug that is rapidly converted to dabigatran) at 110 or 150mg twice daily in a blinded fashion, with warfarin adjusted to an INR of 2-3 in a non-blind study mode.

During a mean follow-up of 2 years, the annual rates of the primary variable (stroke or systemic embolism) were 1.53% for the low dose of dabigatran, 1.11% for the high dose and 1.69 % for warfarin. The relative risks against warfarin were 0.91 (0.74-1.11) for the low dose ($P<.001$ for non-inferiority) and 0.66 (0.53-0.82) for the group taking the high dose ($P<.001$ for superiority).

The annual mortality rate was 3.75% and 3.64% for the groups with low and high doses, respectively, compared with 4.13% for warfarin. The relative risk was 0.91 (0.8-1.03) for the low dose ($P=.13$) and 0.88 (0.77-1) for the high dose ($P=.051$).

Annual rates of myocardial infarction were 0.72%, 0.74% and 0.53% for the low dose of dabigatran, high dose of dabigatran and warfarin, respectively. The risk trend was higher for the low dose of dabigatran at 1.35 (0.98-1.87: $P=.07$) and significantly higher in the high dose group, 1.38 (1-1.91; $P=.048$).

Hemorrhagic stroke rates were 0.12% per year ($P<.001$) and 0.1% per year ($P<.001$) for the groups with low and high doses, respectively, and 0.38% for warfarin. The rates of severe haemorrhage were 2.71 ($P=.003$ against warfarin) for the low dose, 3.11 (not significant against warfarin) for the high dose and 3.36 for warfarin, as shown in table 1.

The number of patients who had to stop treatment with dabigatran was significantly higher, perhaps due to dyspepsia, the main side effect that occurred most frequently with dabigatran (11.8% and 11.3% per year, respectively) than with warfarin (5.8% per year).

The study included 3,623 patients with a prior history of stroke or TIA (about 20%). The results were similar to the general study for stroke or systemic embolism (annual rate for warfarin, 2.74%; dabigatran 110 mg, 2.32%; dabigatran 150 mg, 2.07%), with no significant differences for patients with or without a prior history of stroke/TIA ($P=.34$), albeit with wide confidence margins. There was a significant difference with a lower risk of intracranial haemorrhage and haemorrhagic stroke for dabigatran at low and high doses. The size of the subgroup does not have statistical power to demonstrate superiority over warfarin.[62]

Doubts about the study include the fact that the design was open, but it was blind for the evaluators, follow-up was short (2 years), absolute risk reduction was small, there was a lack of antidote and a slight increase of myocardial infarction. These potential objections are overcome by the drug profile, especially by the high number of patients with AF who currently do not have adequate treatment because of problems with vitamin K antagonists.

Low doses of dabigatran (similar efficacy with less risk of haemorrhage than warfarin) would be indicated in patients

Table 1 Results from the RE-LY[61] study

	D 110 (n=6.015), episodes (annual %)	D 150 (n=6.076), episodes (annual %)	W (n=6.022), episodes (annual %)	D110 vs W		D150 vs W	
				HR (95% CI)	P	HR (95% CI)	P
Systemic stroke or embolism	182 (1.53)	134 (1.11)	199 (1.69)	0.91 (0.74-1.11)	< 0.001[a]	0.66 (0.53-0.82)	< 0.001[b]
Total stroke	171 (1.44)	122 (1.01)	185 (1.57)	0.92 (0.74-1.13)	0.41	0.64 (0.51-0.81)	< 0.001
Deadly or incapacitating stroke	112 (0.94)	80 (0.66)	118 (1)	0.94 (0.73-1.22)	0.65	0.66 (0.5-0.88)	0.005
Myocardial infarction	86 (0.72)	89 (0.74)	63 (0.53)	1.35 (0.98-1.87)	0.07	1.38 (1-1.91)	0.048
Vascular death	289 (2.43)	274 (2.28)	317 (2.69)	0.9 (0.77-1.06)	0.21	0.85 (0.72-0.99)	0.04
Total death	446 (3.75)	438 (3.64)	487 (4.13)	0.91 (0.8-1.03)	0.13	0.88 (0.77-1)	0.051
Severe haemorrhage	322 (2.71)	375 (3.11)	397 (3.36)	0.8 (0.69-0.93)	0.003	0.93 (0.81-1.07)	0.31
Intracranial haemorrhage	27 (0.23)	36 (0.3)	87 (0.74)	0.31 (0.2-0.47)	< 0.001	0.4 (0.27-0.6)	< 0.001

D 110: dabigatran 110mg; D 150: dabigatran 150mg; W: warfarin.
[a]For non-inferiority, P=0.34.
[b]For non-inferiority, P<.001.

at increased risk of haemorrhage[38] and with predisposing factors such as advanced age, poorly controlled hypertension, history of previous brain haemorrhage, neuroimaging (CT/MRI) of cerebral leukoaraiosis and microhaemorrhage and high INR.

High doses of dabigatran (higher efficacy with a similar risk of haemorrhage to warfarin) would be indicated in patients with increased cardioembolic risk, as well as in patients with problems with subtherapeutic INR or unjustifiably non-anticoagulated, or with problems with vitamin K antagonists. In the case of patients with prior cerebral ischemia, there is no defined dose, although the same general considerations could be adopted.

According to these data, it is very likely that dabigatran indication is approved for the prevention of stroke, thus helping many people with AF to be better controlled and with a proper treatment regime. Doctors will implement indications better and patients will improve adherence, which will result in the prevention of many strokes and their consequences.

Lastly, new anticoagulant drugs under study, such as the factor Xa inhibitors rivaroxaban apixaban or edoxaban or others, could be added to the arsenal of antithrombotic therapy for AF.[63]

It is alarming to think about the consequences of millions of people with AF with an inadequate diagnosis or stroke prevention, but the advances described open a picture of hope.

Key Points

—A proper aetiological diagnosis of cerebral ischemia is needed, as well as an increase in the detection of atrial fibrillation in ischemic stroke, based on an efficacy of antithrombotic drug prevention that is very different between antiplatelets and anticoagulants.

– Dronedarone is the first antiarrhythmic drug that reduces vascular mortality and stroke beyond standard therapy, and neurologists should be involved in its indications and management.

—Statins and blockage of the renin-angiotensin system may improve the management of patients with atrial fibrillation and stroke by reducing *de novo* atrial fibrillation or its recurrence.

—If oral anticoagulation is contraindicated, the combination of clopidogrel and aspirin may be an acceptable alternative. The WATCHMAN device can also be an alternative in highly selected patients with absolute contraindications to oral anticoagulation.

—Dabigatran, a direct thrombin inhibitor, is an effective and safe drug in the prevention of cardioembolic stroke by atrial fibrillation; it also minimises the problems of vitamin K antagonists, which it will most likely displace.

—Neuroscientists are crucial in the implementation of oral anticoagulation recommendation in the prevention of cardioembolic cerebral ischemia at any age to avoid suffering and dependence. Consequently, we have a great responsibility to improve the prognosis for millions of

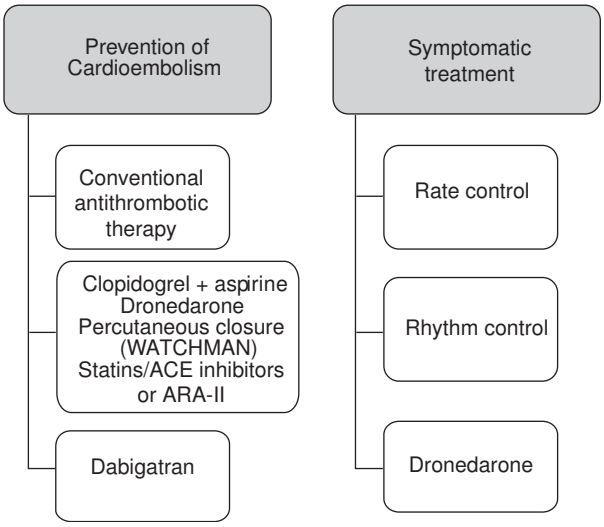

Figure 1 Therapeutic advances in the prevention of cardioembolic cerebral ischemia by atrial fibrillation.

patients with cerebral ischemia and atrial fibrillation, who are currently following inadequate treatments.

—It is necessary to amend the guides according to these developments; the outlook remains open (fig. 1).

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