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EDITORIAL

Atrial fibrillation subtypes, risk of stroke, and antithrombotic therapy

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This editorial refers to 'Should we abandon the common practice of withholding oral anticoagulation in paroxysmal atrial fibrillation?'† by R. Nieuwlaat *et al.*, on page 915

Despite a significant decline in the last 50 years, stroke remains the third leading cause of mortality in men and the second in women.[1] Stroke also represents the leading cause of disability and the second of dementia, with a tremendous impact on the affected patients and their relatives. Approximately one-third of ischaemic strokes are caused by an embolus originating from the heart, and in the majority of these cases atrial fibrillation is responsible for the thromboembolic event. This proportion may be even higher, as the role of atrial fibrillation in the pathogenesis of stroke may be underestimated. In fact, the observation of sinus rhythm on the surface electrocardiogram at hospital admission for stroke, in the absence of clinical history of atrial fibrillation, does not rule out the possibility of a new-onset and self-terminating arrhythmic episode that preceded the occurrence of neurological symptoms. Close electrocardiographic monitoring may increase the detection of atrial fibrillation among stroke patients, but at present it can be performed only in the limited number of available stroke units.

Atrial fibrillation is indeed one of the most important risk factors for stroke.[2] The rate of ischaemic stroke among patients with atrial fibrillation averages 4.5% per year, which is 4–5 times more than in patients without atrial fibrillation, and the risk significantly increases with age.[3] After 80 years of age, the annual rate of stroke in patients with atrial fibrillation reaches the staggering figure of 25%.[4] Stroke due to atrial fibrillation is also associated with larger cerebral infarcts and a higher neurological impairment. As a consequence, the outcome of patients with atrial fibrillation who suffer a stroke is worse, as they show a greater degree of disability. The risk of stroke in patients with atrial fibrillation increases in the presence of additional factors, such as history of hypertension, diabetes, heart failure, and previous transient ischaemic attack (TIA) or stroke.[5,6] Recent data also suggest that women with atrial fibrillation have a higher risk of stroke than men, independently of age and additional risk factors.[7]

The rate of embolic events originating from the atrium in patients with atrial fibrillation increases with the reduction of left atrial appendix flow velocity and the presence of echocontrast at transoesophageal ultrasound examination.[8] Unfortunately, the duration of atrial fibrillation which may be associated with the development of a thrombus in the atrium is extremely short, as this event may occur within 24–48 h. As a consequence, even a short episode of atrial fibrillation may significantly increase the thrombogenic substrate and the risk of stroke during the arrhythmic episode, at the time of spontaneous sinus rhythm restoration and also in the following days. A relationship between the number of additional risk factors in patients with atrial fibrillation and the presence of echocontrast or reduced flow velocity in the left atrial appendix has been demonstrated,[9] suggesting that factors such as hypertension, diabetes, and heart failure may influence the complex thromboembolic mechanisms.

Antithrombotic therapy prevents stroke in patients with atrial fibrillation. A recently updated meta-analysis[10] which included 29 randomized clinical trials comprising 28 044 patients has shown that oral anticoagulants and antiplatelet agents were significantly effective for both primary and secondary prevention of stroke, with a 64 and 22% reduction of relative risk, respectively. In the 12 trials which compared anticoagulant therapy with antiplatelet agents in 12 963 patients, warfarin was more effective than aspirin, with a relative risk reduction of 39%. It has to be noted that these effects were observed in both permanent and paroxysmal atrial fibrillation. However, the similar efficacy of therapy in the different subtypes of atrial fibrillation is not completely taken into account in clinical practice, as anticoagulants are frequently withdrawn in patients with paroxysmal atrial fibrillation. This choice is usually made because of the apparent absence of recurrence of atrial fibrillation. However, episodes of atrial fibrillation may be completely asymptomatic and go unrecognized, particularly in patients who are treated with antiarrhythmic agents able to maintain a normal heart rate even in the case of recurrence.

The report of Nieuwlaat *et al.*[11] deals with the important issue of the relationship between the type of atrial fibrillation, i.e.

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permanent, persistent, or paroxysmal, and thromboembolic events. The authors performed an interesting analysis of the data from the observational study 'Euro Heart Survey on Atrial Fibrillation'. The Euro Heart Surveys are targeted to assess the use of cardiovascular diagnostic and therapeutic procedures in the various European countries. The survey on atrial fibrillation involved >4000 patients, enrolled in different European countries, and reflects the clinical practice followed by European physicians in the management of patients with atrial fibrillation. The occurrence of stroke and thromboembolism during a 1-year follow-up was analysed according to the type of atrial fibrillation. Patients with paroxysmal atrial fibrillation had a risk for stroke comparable with those with persistent or permanent atrial fibrillation.

The results of the study by Nieuwlaat *et al.* are in agreement with those recently obtained from an analysis of a large trial on antithrombotic therapy in atrial fibrillation.[12] The incidence of thromboembolic events was similar in patients with paroxysmal atrial fibrillation when compared with those with persistent or permanent atrial fibrillation enrolled in the ACTIVE study (Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events), a trial aimed at comparing warfarin with combined antiplatelet therapy with aspirin and clopidogrel. The risk for thromboembolic events in patients with any type of atrial fibrillation could be significantly lowered with warfarin, which was more effective than the combination of antiplatelet agents.

The findings of Nieuwlaat *et al.* obtained prospectively in a large European population of patients with atrial fibrillation, together with other similar observations, support the recommendation that the type of atrial fibrillation should not influence the choice of appropriate antithrombotic therapy. The choice of antithrombotic therapy should rather be guided by the presence of additional risk factors for stroke. High-risk atrial fibrillation patients show a larger relative risk reduction with oral anticoagulation compared with aspirin, whereas the relative risk reductions are smaller in atrial fibrillation patients with lower stroke rates. The absolute increases in major haemorrhages which may be associated with antithrombotic therapy are small but not negligible. Accordingly, the beneficial effect of oral anticoagulation should be weighed against the risk of bleeding. Thus, quantifying the risk of stroke is crucial for determining which atrial fibrillation patients would benefit most from anticoagulant therapy. Different stroke risk stratification schemes have been proposed for atrial fibrillation patients.[13] In the $CHADS^2$ score (acronym derived from the individual stroke risk factors: Congestive heart failure, Hypertension, Age >75 years, Diabetes, and prior Stroke or TIA), 2 points are given for prior stroke or TIA, and 1 point is assigned for each of the other factors. The most recent 2006 AHA/ACC/ESC Guidelines for the management of patients with atrial fibrillation[14] recommend antithrombotic therapy for the prevention of stroke on the basis of the $CHADS^2$ risk score. In patients with permanent, persistent, or paroxysmal atrial fibrillation and a $CHADS^2$ score $\geq$2, anticoagulant therapy with an international normalized ratio (INR) between 2.0 and 3.0 is indicated. The study by Nieuwlaat *et al.* allows the additional suggestion that anticoagulant therapy should not be withdrawn in patients with paroxysmal atrial fibrillation. There are no robust data to establish a threshold of duration and frequency of atrial fibrillation episodes for the stratification of risk of thromboembolic events, although ongoing studies may provide novel insights. Accordingly, at present, the suggestion of not withholding anticoagulant therapy should be followed for all patients with paroxysmal atrial fibrillation. However, the management of oral anticoagulant therapy in clinical practice is not an easy task and many patients are not adequately treated. As alternative therapies are not available at the present time, a strict control of coagulation during anticoagulant therapy is necessary in order to maintain effective antithrombotic protection and reduce the bleeding risk. A recent study has shown that the addition of pharmacogenetic factors, such as polymorphisms of drug metabolism enzymes, to a clinical algorithm for the management of anticoagulant therapy improved the accuracy and efficiency of warfarin dose initiation.[15] Efforts should be made to increase the number of patients with atrial fibrillation who receive the appropriate antithrombotic therapy for stroke prevention. The analysis of the Euro Heart Survey on Atrial Fibrillation performed by Nieuwlaat *et al.* constitutes an important contribution for the management of antithrombotic therapy in clinical practice, and may stimulate further research.

Conflict of interest: none declared.

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CLINICAL VIGNETTE

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Ischaemic stroke and myocardial infarction in a Caucasian patient with Moya–Moya disease

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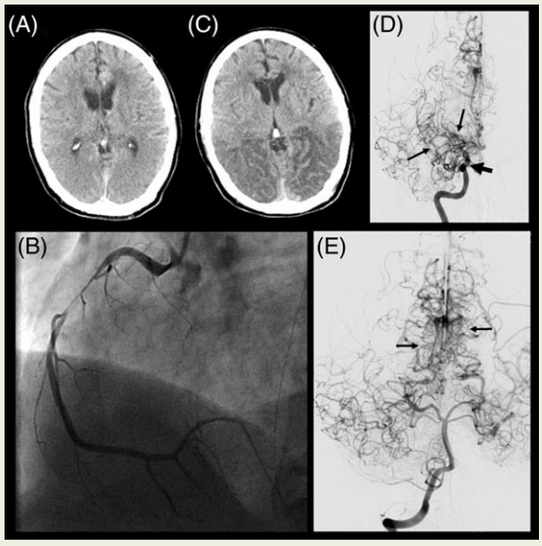
A 48-year-old male was admitted to our department after falling backwards down the stairs and resuscitation as a result of ventricular fibrillation. On admission, a CT scan was performed that ruled out intracranial bleeding, but showed posterior swelling (Panel A), and a stable type-II fracture of the odontoid process of the axis (not shown). Myocardial enzymes were elevated. Coronary angiography showed a single, >90% diameter, flow-limiting stenosis of the proximal right coronary artery (Panel B), which was treated with percutaneous coronary intervention. On the following day, severe visual impairment was observed. A second CT scan showed extensive bilateral posterior cerebral infarction (Panel C). Cerebral angiography revealed terminal post-communical occlusion of both internal carotid arteries (Panel D), a dominant right vertebral artery (Panel E) and net-like collaterals typical for Moya–Moya disease (Panels D and E). We hypothesize that bilateral posterior stroke in this patient is because of trauma-related transient insufficiency of the posterior circulation in the presence of diminished collateral blood flow from the circle of Willis because of Moya–Moya disease. Myocardial ischaemia as a result of obstruction of the proximal right coronary artery in the absence of other coronary stenoses may also be related to Moya–Moya disease. Coronary artery obstruction and coronary spasm have been observed in the presence of Moya–Moya disease, suggesting an underlying systemic arterial disorder. Moya–Moya disease is characterized by bilateral stenosis or occlusion of the terminal portions of the internal carotid arteries accompanied by net-like collateral vessels in the basal ganglia. Its aetiology is still unknown.



Panel A. Initial cerebral CT scan ruling out intracranial bleeding, but showing posterior swelling.

Panel B. Angiogram of the right coronary artery showing a single, >90% diameter stenosis in segment 1.

Panel C. Cerebral CT scan on the day after admission showing large bilateral posterior infarction of the brain.

Panel D. Cerebral angiogram (anterior–posterior projection) after injection of contrast agent in the right internal carotid artery. The big arrow points to the occlusion of the post-communical internal carotid artery. The smaller arrows point to the net-like collaterals typical for Moya–Moya disease.

Panel E. Cerebral angiogram obtained (anterior–posterior projection) after injection of contrast agent in the dominant right vertebral artery. Cerebral perfusion is largely dependent on the posterior circulation. Black arrows are pointing to the net-like collaterals.