

President's Page

Atrial Fibrillation: Building Walls and Breaking Down Bridges

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Ἀσκέειν, περὶ τὰ νοσήματα, δύο, ὠφελέειν, ἢ μὴ βλάπτειν
 With regard to diseases, strive for two things: to do good, or to do no harm

Hippocrates of Kos (460–377 BC)

Atrial fibrillation, with a prevalence of around 1% in the general population, is the most common arrhythmia and, whether paroxysmal or permanent, is the main cause of stroke.^{1,2} Indeed, in the case of atrial fibrillation of non-valvular cause, two thirds of strokes are the result of cardiac emboli. Anatomical, pathological and echocardiographic studies have shown that approximately 90% of these strokes are the result of thrombi originating from the left atrial appendage. Unfortunately, strokes from cardiac emboli are particularly catastrophic, with a very bad prognosis. Therefore, there is an urgent need of strategies for the prevention, or at least reduction, of these strokes. Anticoagulant medication, represented for many years mainly by the vitamin K inhibitor warfarin, has proved especially effective in reducing ischaemic strokes. However, it has many limitations, mainly because of its relative or absolute contraindications – principally linked with an increased risk of haemorrhage – but also because of poor patient compliance with the treatment. It has been reported that after four years only 40% of patients continue to take warfarin, while only 60% of repeated INR measurements remain within the therapeutic range. Furthermore, nowadays, with the frequent use of double antiplatelet medication following percutaneous reperfusion interventions, the need for the coadministration of warfarin increases the risk of haemorrhage even more.³

Because of these difficulties, the appearance of new oral anticoagulants (NOACs) was to be expected. These drugs have now been evaluated in large-scale randomised trials with a total participant population of more than 50,000. Although the majority of

these studies showed that NOACs were non-inferior and/or superior to warfarin in reducing strokes, the risk of haemorrhagic complications remains high. The two direct factor Xa inhibitors (rivaroxaban, apixaban) and the direct factor IIa inhibitor dabigatran, though significantly reducing the risk of haemorrhagic stroke, were not found to have a comparable effect on the reduction of major haemorrhages, which showed an annual incidence of 2-3%, while the incidence of small haemorrhages exceeded 10%. Furthermore, NOACs so far have no antidotes, which leads to significant problems in cases of severe haemorrhage, or if there is a need for immediate cessation of therapy because of emergency surgery. The advantage of NOACs is that they do not need regular monitoring, which makes them better tolerated compared to warfarin, although it makes evaluation of the therapeutic result by physicians more difficult.

So far, no direct comparisons between NOACs are available. However, a recent meta-analysis of four studies that compared apixaban, dabigatran and rivaroxaban with warfarin in a total of 44,733 patients⁴ showed that dabigatran reduced the composite endpoint of systemic emboli and stroke compared to rivaroxaban, while apixaban compared to rivaroxaban and dabigatran significantly reduced the risk of gastrointestinal haemorrhage.⁵

Apart from pharmaceutical treatment for the prevention of systemic emboli arising from atrial fibrillation, invasive strategies have recently recorded some developments, mainly ligation and exclusion of the left atrial appendage, either surgically or percutaneously.^{6,7} Although this appears to be an attractive approach, especially in patients who cannot tolerate

oral anticoagulants, its clinical application has proved to be rather difficult, mainly because of its invasive nature and the problems involved in carrying out large-scale randomised trials. At least four devices for percutaneous exclusion of the atrial appendage are commercially available: a) the PLAATO (percutaneous left atrial appendage transcatheter occlusion) device,⁸ b) the Watchman device, c) the Amplatzer cardiac plug, and d) the Lariat device. Since the PLAATO device has been withdrawn from the market because of an increased rate of stroke and pericardial effusion,⁹ the Watchman device is the only one that has so far shown encouraging results in the sole randomised clinical trial in this category, PROTECT-AF.¹⁰ In this study 700 patients with non-valvular atrial fibrillation and a CHAD₂DS₂-VASc score >1 were randomised to either placement of a Watchman or warfarin administration. The device proved non-inferior to warfarin as regards the composite endpoint of effectiveness (stroke, systemic emboli, cardiovascular mortality),^{11,12} although the safety endpoint (a composite of major haemorrhage, pericardial effusion, device embolisation, and periprocedural stroke) showed the device at a disadvantage.¹³ In 2011, the long-term combined data from the PROTECT-AF trial and the parallel CAP (continued access protocol) registry were announced, including a total of 1000 patients. The investigators observed a significant reduction in adverse events associated with the intervention. The rates of severe pericardial effusion and periprocedural stroke decreased significantly from the main study to the CAP registry, from 5% to 2.2% and from 0.9% to 0%, respectively. In results stretching over a time interval of more than two years, the Watchman device remained non-inferior to warfarin, with an event rate of 3% per 100 person-years compared to 4.3% in the warfarin group. The periprocedural adverse event rate, though improved, remained higher in the device group (5.5% versus 3.6%). In addition, placement of the device was associated with a significant improvement in quality of life parameters at 12 months compared to warfarin.¹⁴

The Amplatzer atrial septal defect closure device has so far been used in a limited number of patients for the exclusion of the left atrial appendage and has proved to be extremely safe.¹⁵ The Amplatzer cardiac plug is a specialised device, specially designed for the exclusion of the left atrial appendage, that has already been evaluated in clinical trials.¹⁶ This device is constructed from a nickel-titanium alloy (nitinol) mesh and consists of a left atrial disc and a dis-

tal lobe that is connected with the atrial disc by a narrow neck. The distal lobe consists of six pairs of pins that are specially designed to increase its stability within the appendage. This device is smaller than the Watchman and may be more effective in cases with a left atrial appendage of complex morphology. Animal experiments have shown that its placement may be performed with efficacy and safety.¹⁷

In recent years atrial fibrillation has attracted a great deal of research attention. The future of the pharmaceutical and interventional therapeutic approaches described above is sure to be exciting. In any case, the existence of multiple reliable therapeutic options is sure to benefit our patients.

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