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Management of atrial fibrillation

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Abstract

Atrial fibrillation (AF) is associated with increases in the risk of mortality, congestive heart failure, and stroke. Medical treatment is aimed at preventing thrombo-embolic complications and reducing symptoms and consequences related to the arrhythmia. In the first section of this review, we discuss the principles of mainstream oral anticoagulant therapy and the possible advantages of the new oral anticoagulants. In the second section, we review the catheter ablation approaches to paroxysmal and persistent/long-standing AF, their results, and the current application of new catheters.

Introduction

AF is the most common cardiac arrhythmia, with an estimated risk of development during lifetime of 1 in 4 men and women with at least 40 years of age [1-3]. The clinical interest in this condition derives from the fact that it increases the risk of mortality by two-fold, of congestive heart failure by three-fold, and of stroke by five-fold. The treatment of AF has two targets: the prevention of the thrombo-embolic complications and the reduction of symptoms and consequences related to the arrhythmia by rhythm or rate control therapies.

Prevention of thrombo-embolic events

Vitamin K antagonists reduced the relative risk of stroke by 64%, corresponding to an absolute annual risk reduction in all strokes of 2.7% [4]. It is universally recognized that the oral anticoagulation (OAC) is the mainstream therapy for the reduction of thrombo-embolic complications related to AF. Several scores have been developed to identify patients with high risk of thrombo-embolic events and those who need anticoagulation. However, given the high efficacy of OAC and the enormous consequences of strokes, it would be better to change our approach from the identification of many patients who need OAC to the research of the few patients who do not need OAC. Cardiologists should therefore consider the presence of AF itself as an indication to anticoagulation therapy, unless the patient has a truly low risk. The latest European Society of Cardiology Guidelines [5] suggest that, for the correct evaluation of patients with non-valvular AF, the use of the CHA_2DS_2-VASc—Congestive heart failure/left ventricular dysfunction, Hypertension, Age of at least 75 (doubled), Diabetes, Stroke (doubled)-Vascular disease, Age 65 to 74, and Sex category (female)—score [6] is more sensible compared with the previously used $CHADS_2$ score.

Patients with AF who have at least one stroke risk factor are recommended to receive OAC with either well-controlled vitamin K antagonist therapy—international normalized ratio (INR) 2-3, with more than 70% of time in the therapeutic range—or one of the new oral anticoagulants (NOACs) [5]. Only patients with lone AF who are less than 65 years old have very low absolute stroke rates and do not require OAC.

The OAC usually revives in the physician's mind the ghost of major bleeding; this fear is the main reason for the frequent denial of such an effective therapy to a high number of patients. The Guidelines suggest the assessment of the bleeding risk in all patients with AF with the HAS-BLED [5]—Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (e.g. age more than 65 years and frailty), Drugs/alcohol concomitantly—score [7]. The score should be used to balance the risk of stroke against potential major bleeding events; however, a high-risk score should not exclude patients from OAC, but favor the identification and correction of potentially reversible risk factors, such as uncontrolled blood pressure, concomitant use of aspirin/non-steroidal anti-inflammatory drugs, and labile INRs.

In patients who are not candidates for OAC, aspirin has been widely considered a good surrogate therapy with fewer side effects. The weapon used in this battle, however, appears not to be pathophysiologically adequate to the setting; in fact, thrombi in patients with AF are predominantly fibrin-rich (the so-called "red clots"), while thrombi found in coronary artery lesions tend to be platelet-rich ("white clots") [8]. Therefore, such an effective therapy in athero-thrombotic vascular disease becomes of limited value in patients with AF. The meta-analysis by Hart *et al*. [4] reviewed seven randomized control trials evaluating the antithrombotic therapy for stroke prevention in non-valvular AF (3990 participants in aspirin-only trials). The result was a reduction of risk of stroke with anti-platelet therapy compared with placebo by 19% (95% confidence interval [CI] –1% to 35%) with a 95% CI that included zero; this raises the possibility of non-significant clinical effect. Aspirin has been frequently used in elderly patients, with the hope of fewer side effects. This belief was not confirmed by the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trial [9], which randomly allocated patients over 75 years of age to receive OAC with warfarin or 75 mg of aspirin daily; in the OAC group, the yearly risk of the primary endpoint (disabling stroke, intracranial hemorrhage, or arterial embolism) was 1.8% and significantly lower than the 3.8% obtained with aspirin; warfarin treatment in the elderly was associated with a 52% relative risk reduction compared with aspirin. Even when a second anti-platelet agent, such as clopidogrel in the ACTIVE-W (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) trial [10], is added, the effect is clearly inferior to the one obtained by the OAC treatment. Following the hypothesis that double anti-platelet association was an effective replacement of OAC, the ACTIVE-A trial [11] randomized 7554 patients with AF to aspirin plus clopidogrel or to warfarin. Double anti-platelet therapy reduced the risk of stroke by 28%, but it increased the risk of major bleeding by 50%. With the advent of NOACs, which promise the efficacy of standard OAC without any increased risk of bleeding, it is not difficult to foresee that both aspirin and the double anti-platelet therapy for AF will become obsolete or restricted to rare cases.

NOACs, in contrast to warfarin (which blocks multiple active vitamin K-dependent coagulation factors), block the activity of one single step in the coagulation process. Dabigatran acts as an oral direct thrombin inhibitor, while rivaroxaban and apixaban both inhibit factor Xa. All NOACs have shown non-inferiority in stroke and systemic embolism prevention, compared with warfarin. In the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial [12], dabigatran 150 mg *bis in die* (twice a day – b.i.d.) was superior to warfarin, with no significant difference in the safety endpoint of major bleeding; the reduced dosage of 110 mg b.i.d. was non-inferior to warfarin, with 20% fewer major bleeds; both dosages were associated with a non-significant increase of 28% in myocardial infarction. In the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thrombotic Events in Atrial Fibrillation) trial [13], apixaban 5 mg b.i.d. reduced the primary endpoint of stroke or systemic embolism by 21% compared with warfarin, with a 31% reduction in major bleeding and a significant 11% reduction in all-cause mortality. Edoxaban, a new factor Xa inhibitor, has completed late-stage clinical assessment [14]. A meta-analysis pooling more than 40,000 patients from four randomized controlled trials comparing NOACs with warfarin has been recently published [15]; compared with warfarin, the NOACs, as a class, reduced all-cause mortality by about 10% in the populations enrolled in the clinical trials. Stroke and systemic embolic events were significantly reduced in patients receiving NOACs; the benefit was driven mainly by substantial protection against hemorrhagic stroke, while they had similar efficacy in the prevention of ischemic stroke. NOACs, however, were associated with an increase in gastro-intestinal bleeding.

Rhythm and rate control strategies

Several trials in recent years tried to assess whether restoration of sinus rhythm offers any advantage compared with the strategy of rate control. Although sinus rhythm restoration is theoretically supposed to be the best option, many studies such as PIAF (Pharmacological Intervention in Atrial Fibrillation) [16], AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) [17], RACE (RAte Control versus Electrical cardioversion for persistent atrial fibrillation) [18], and STAF (Strategies of Treatment of Atrial Fibrillation) [19] failed to report any survival benefit from rhythm-control strategy. Also, in the population of patients with heart failure, no clear benefit was demonstrated for this strategy [20,21]. Later "on treatment" analysis of the AFFIRM trial showed that the presence of sinus rhythm is associated with a lower risk of death [22]; this analysis suggested that the adverse effects of anti-arrhythmic drugs (AADs) overcome the beneficial effects of sinus rhythm restoration; it is also conceivable that the efficacy of currently available AADs is so limited and transient that any positive effect of sinus rhythm does not have enough time to develop.

This raised the interest in other treatments, such as catheter ablation (CA) of AF, whose effects are supposed to be more durable. Wilber *et al*. [23] compared the efficacy of catheter ablation with AAD treatment in treating symptomatic patients with paroxysmal AF who had not responded to at least 1 AAD; the invasive treatment resulted in a longer time to treatment failure (66% of patients in the catheter ablation group remained free from protocol-defined treatment failure compared with 16% of patients treated with AAD therapy) during the 9-month follow-up period [23].

The efficacy of CA is dependent on the type of AF, the presence of cardiac structural heart disease, and co-morbidities. Presence of left atrial scar is an independent predictor of arrhythmia recurrence after the ablation [24]. Magnetic resonance imaging studies demonstrated that recurrence rate after CA is directly related to the amount of left atrial scar [25]: patients with minimal late gadolinium enhancement (8.0% ± 4.2%) have fewer recurrences (14.0%) compared with patients with moderate enhancement (21.3% ± 5.8%, recurrence rate = 43.3%) and patients with extensive enhancement (50.1% ± 15.4%, recurrence rate = 75%). When confirmed by large population studies, the extension of left atrial scar can be included in the pre-operative assessment of AF patients in order to reduce the number of procedures in patients with expected low efficacy.

The best results of the CA procedure are actually obtained in patients with paroxysmal AF in the absence of cardiac structural disease and co-morbidities [26-33]. In those patients, AF is related to the presence of triggers in the pulmonary veins (PVs) [34,35]; therefore, PV isolation is the cornerstone treatment for patients with paroxysmal AF [34,36-38]. In a recent meta-analysis of 19 studies, rates of single-procedure success for paroxysmal AF ablation were 68.6% (95% CI 58.9% to 77.0%) at 1 year, 61.1% (95% CI 49.8% to 71.2%) at 3 years, and 62.3% (95% CI 39.8%to 80.5%) at 5 years [39]. The pooled 12-month success rate for paroxysmal AF ablation after a single procedure was 66.6% (95% CI 58.2% to 74.2%); it increased to 79.0% (95% CI 67.6% to 87.1%) when multiple procedures were used (average number of procedures: 1.45). The most common cause of arrhythmia recurrence is reconduction across PV isolation; Nanthakumar *et al*. [40] found reconduction in 42 of 51 previously isolated veins in 15 patients with recurrent symptoms after a first ablation for paroxysmal AF. In the experience of Verma *et al*. [41], all veins were still isolated in 81% of patients undergoing a repeat procedure after the index ablation; this rate dropped to 5% and 0% in the patients maintaining sinus rhythm on AADs and in patients with arrhythmia despite AADs.

Ablation has been performed for many years with the point-by-point approach with continuous catheter dragging during radiofrequency delivery or by repeated short-time radiofrequency shots. This approach is highly dependent on the operator's skill and the contact between the tip of the catheter and the target tissue; freedom from arrhythmia recurrences is best achieved when ablation lesions are placed with an average contact force (CF) of more than 20 g, and clinical failure is frequent with an average CF of less than 10 g [42,43].

Recently developed catheters allow PV isolation with one or a few shots of radiofrequency, cryo-energy, or laser pulses. Medtronic PVAC (Medtronic Ablation Frontiers, Carlsbad, CA, USA) and nMARQ™ (Biosense Webster, Diamond Bar, CA, USA) catheters have a circular shape that fits with pulmonary veins ostia; radiofrequency can be delivered simultaneously by a variable number of electrodes [44,45]. The Arctic Front Advance™ Cardiac CryoAblation Catheter (Arctic Front; Medtronic) consists of a balloon that can be placed at each PV ostium in order to obtain PV occlusion; ablation is then performed by cryo-energy [46,47]. HeartLight™ (CardioFocus Inc., Marlborough, MA, USA) is a visually guided laser ablation catheter with a variable-diameter balloon that accommodates a 2-Fr endoscope; it provides real-time visualization of the balloon contact and blood during the ablation. In a multicenter experience enrolling 200 patients with paroxysmal AF, it showed an efficacy similar to that of radiofrequency ablation [48]. Reported major complications were cardiac tamponade (2%) and phrenic nerve palsy (2.5%). These four new catheters have the potential advantage of faster and technically easier procedures [49].

PV isolation is still mandatory for the treatment of persistent and long-standing AF. However, recurrent and chronic AF induces progressive electrical and tissue structural remodeling, thus making AF a self-perpetuating disease [50]; to interrupt this looping process, the ablation procedure in non-paroxysmal AF patients usually requires some kind of substrate modification. Three approaches were developed: linear lesions, complex fractionated atrial electrogram (CFAE) ablation, and electrical rotor elimination. Linear lesions have been applied on the left atria roof and on the mitral isthmus with the aim of preventing macro-re-entry-dependent arrhythmias; several studies reported that additional lines improve the efficacy of the procedure [51,52]. The downside of this approach becomes evident when the lines are not electrically continuous; in those cases, atrial tachycardia frequently develops [53]. In order to reduce macro-re-entry arrhythmias recurrences, the operator should validate the presence of a bidirectional conduction block across all ablation lines [54]. CFAE ablation was proposed by Nademanee *et al.* [55]; it can be used alone or in combination with PV isolation. Manifest controversies still exist concerning the usefulness of this approach because it frequently requires wide left atrial ablation, and it is hampered by a high post-procedural atrial tachycardia rate. In the RASTA (randomized ablation strategies for the treatment of persistent atrial fibrillation) study [56], 1-year AF-free survival was significantly lower in patients treated with the standard approach (PV isolation + ablation of documented non-PV triggers identified by a standard stimulation protocol) plus CFAE ablation compared with the standard approach alone or the standard approach combined with the empirical ablation at common non-PV trigger sites. Recent evidence demonstrated that electrical rotors have a key role in sustaining AF in humans. Narayan *et al.* [57] used a 64-pole basket catheter to record monophasic action potentials in human left atria. A computational approach was used to analyze the repolarization and conduction dynamics with the aim of reconstructing spatio-temporal AF maps; ablation guided by identification of focal impulses and rotors improved the overall procedure success [58,59]. Results of catheter ablation in patients with non-paroxysmal AF are still not satisfactory. In the meta-analysis by Ganesan *et al.* [39], rates of single-procedure success for non-paroxysmal AF ablation were 50.8% (95% CI 34.3% to 67.2%) at 1 year and 41.6% (95% CI 24.7% to 60.8%) at 3 years. The pooled 12-month success rate after a single procedure was 51.9% (95% CI 33.8% to 69.5%); it increased to 77.8% (95% CI 68.7% to 84.9%) when multiple procedures were used (average number of procedures: 1.67).

Abbreviations

AAD, anti-arrhythmic drug; ACTIVE-W, Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events; AF, atrial fibrillation; AFFIRM, Atrial Fibrillation Follow-up Investigation of Rhythm Management; b.i.d., *bis in die* (twice a day); CA, catheter ablation; CF, contact force; CFAE, complex fractionated atrial electrogram; CI, confidence interval; INR, international normalized ratio; NOAC, new oral anticoagulant; OAC, oral anticoagulation; PV, pulmonary vein.

Disclosures

The authors declare that they have no competing interests.

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