

Progress in Treatment of Atrial Fibrillation

Lili Jin¹, Ruiqin Xie^{2*}

¹Hebei Medical University, No.361 Zhongshan East Road, Shijiazhuang, China

²Second Affiliated Hospital, Hebei Medical University, No.215 Heping West Road, Shijiazhuang, China

Abstract

Atrial fibrillation (AF) is the most common supraventricular arrhythmia in clinical practice. Rapid, unordered atrial electroactivity is the characteristic of AF. The main manifestations of the electrocardiogram are P wave disappeared and RR interval irregular absolutely (except for the three degree atrioventricular block). Atrial irregular contractions cause atrial thrombosis. The irregular contraction of ventricle leading to a decrease in cardiac pump function, which can seriously affect ventricular systolic and diastolic function. In 2010, about 33.5 million people suffered from AF around the world. In the European Union, there are an estimated 14 million to 17 million people with AF by 2030. In the United States, there are about 27 million to 61 million AF patients. With the trend of population aging in recent years, the incidence of AF increases gradually. AF is not only a great challenge for cardiologists, but also a hot research topic. The following review is in the treatment progress of AF in recent years.

Introduction

Application of non-vitamin K antagonist oral anticoagulants (NOACs)

The factor Xa inhibitors and the direct thrombin inhibitor have been gradually applied in clinic in recent years. The NOACs have the advantages of less interaction with other drugs and food, without frequent anticoagulation monitoring, compared with the traditional vitamin K antagonists. In the 2014 AHA/ACC/HRS guidelines and the 2016 ESC guidelines, the NOACs are preferred to warfarin for the patients (non-valvular AF) with a CHA₂DS₂-VASc score of 2 or more [1-5].

Rivaroxaban, Apixaban and Edoxaban are highly selective, direct factor Xa inhibitors, which inhibiting thrombin formation and thrombosis. A large scale, randomized clinical research (ROCKET-AF) showed, Rivaroxaban was non-inferior to warfarin for prevention of stroke and systemic embolism, and reduced major bleeding events significantly [6]. The ARISTOTLE study revealed, compared with warfarin, Apixaban reduced stroke or systemic embolism, combined with reduction in all-cause mortality and major bleeding [7]. In the ENGAGE AF-TIMI 48 trial, Edoxaban 60 mg everyday was non-inferior to warfarin, which reduced stroke or systemic embolism and reduced major bleeding events significantly [8]. The Hokusai-VTE study showed, the incidence of clinical bleeding in the edoxaban group was lower than the warfarin group [9].

Dabigatran is direct thrombin inhibitor. Multicenter, large-scale, randomized phase III clinical trial (RE-LY) showed, Dabigatran 110 mg twice everyday was non-inferior to warfarin for prevention of stroke and systemic embolism, combined with less major bleeding events [10]. Sub-group analyses showed that the dose of 110 mg was more suitable for patients with age older than 75 and moderate renal insufficiency.

The role of Radiofrequency Catheter Ablation (RFCA) has been Significantly Improved

The RFCA of AF has been developed rapidly and widely used in clinic in recent years. In the 2006 AHA/ACC/ESC guidelines, patients screened for RFCA depended on the type of AF, age, structural heart disease and patients' choice. The 2014 AHA/ACC/HRS AF management guidelines recommended: for patients with symptomatic paroxysmal AF, RFCA is a reasonable initial treatment (IIa); for

patients with symptomatic persistent AF, it is reasonable to choose RFCA after at least 1 antiarrhythmic drug is refractory (IIa) [11]. The 2016 ESC guidelines for the management of AF pointed out that RFCA of AF should be considered as first-line therapy to prevent recurrent AF and to improve symptoms in selected patients with symptomatic paroxysmal AF as an alternative to antiarrhythmic drugs therapy, considering patient choice, benefit, and risk (IIa, B) [12] (Table 1).

Pulmonary vein isolation (PVI) is the footstone of RFCA. PVI had been shown to be an effective ablation strategy in patients with paroxysmal AF. But might not be as effective by itself in patients with persistent or long-standing persist AF [13]. A recently study showed, among patients with persistent AF, there was no reduction in the rate of recurrent AF when either linear ablation or ablation of complex fractionated electrograms was operated in addition to PVI [14]. Catheter ablation techniques for persist or long-standing persist AF including linear lesions, modulation of rotors and focal impulses, complex fractionated electrograms and substrate modification. However, the effect of various strategies still needs to be verified by large-scale clinical trials [15].

Rapid Development of Cryoballoon Ablation

Cryoballoon ablation is a safe and effective treatment for paroxysmal AF [16,17]. Because of less dependence on the operator's technique, and less discomfort of the patient's, cryoballoon ablation has been developed rapidly in recent years. The first-generation of cryoballoon has four injection ports with less distal location of injection tubes. The freezing zone was annular. In 2012, the second-generation cryoballoon was approved by the US Food and Drug Administration (FDA). It has 8 injection tubes, compared with 4 in the first-generation cryoballoon. And a more distal location of the injection ports on the catheter shaft.

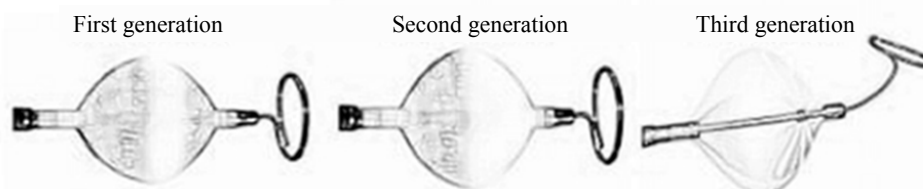
***Corresponding author:** Ruiqin Xie, Second Affiliated Hospital, Hebei Medical University Shijiazhuang, China, Tel: + 8615803212537; E-mail: 13230178060@163.com

Received November 01, 2017; **Accepted** November 20, 2017; **Published** November 25, 2017

Citation: Jin L, Xie R (2017) Progress in Treatment of Atrial Fibrillation. J Interv Gen Cardiol. 1: 104.

Copyright: © 2017 Xie R, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

The guidelines	Changes
2006 AHA/ACC/ESC guidelines	Patients screened for RFCA depended on the type of AF, age, structural heart disease and patients' choice.
2014 AHA/ACC/HRS guidelines	For patients with symptomatic paroxysmal AF, RFCA is a reasonable initial treatment (IIa); For patients with symptomatic persistent AF, it is reasonable to choose RFCA after at least 1 antiarrhythmic drug is refractory (IIa).
2016 ESC guidelines	RFCA of AF should be considered as first-line therapy to prevent recurrent AF and to improve symptoms in selected patients with symptomatic paroxysmal AF as an alternative to antiarrhythmic drugs therapy, considering patient choice, benefit, and risk (IIa,B).

Table 1: The changes of guidelines for radiofrequency catheter ablation (RFCA).**Figure 1:** The first-generation of cryoballoon has four injection ports with less distal location of injection tubes. The freezing zone was annular. The second-generation cryoballoon has 8 injection tubes. And a more distal location of the injection ports on the catheter shaft. The freezing zone was broader and homogeneous. The third-generation cryoballoon with 40% reduction in the length of the catheter tip.

The freezing zone was broader and homogeneous. The third-generation cryoballoon got approval from the FDA in May 2015, for the treatment of patients with recurrent, drug refractory, symptomatic, paroxysmal AF, with 40% reduction in the length of the catheter tip [18] (Figure 1).

Studies have shown that, the rate of patients free from AF is 60%-69% during a follow-up period of 12 months after cryoballoon ablation [19-21]. Ciconte et al. reported the success rate was similar, after 12 months of follow-up observation, between cryoballoon ablation group and RFCA group for patients of persistent AF [21]. This result may be related to the structure of the pulmonary vein itself. In most patients, the anterior-posterior diameters of pulmonary veins are smaller than the upper-lower diameters. Therefore, the cryoballoon caused damage to the posterior left atrium wall during the ablation of pulmonary veins [22]. The expanded freezing zone may be the areas that many stable rotors located in, thus benefiting the patients [23,24]. However, there is still lack of large-scale clinical trials to verify the efficacy of cryoballoon ablation in patients with persistent AF.

Percutaneous Left Atrial Appendage Closure is Emerging Gradually

The left atrial appendage is the primary source of thromboembolism in patients with non-valvular AF, which plays an important role in the prevention of stroke and systemic embolism for patients with high bleeding risk or contraindication of OACs. Surgical left atrial appendage closure (or resection) has been going on for decades. Percutaneous left atrial appendage closure is emerging gradually in recent years. In the 2012 ESC guidelines for the management of AF pointed out that patients with high risk of stroke and could not take any long-time anticoagulants could choose left atrial appendage closure (IIb, B) [25]. The 2016 ESC guidelines recommend anticoagulant therapy is still needed to prevent stroke for patients after surgical left atrial appendage occlusion (or resection) (I, B). Patients with AF have long-term anticoagulation for stroke prevention may be considered taboo, left atrial appendage occlusion (IIb,B) [15]. The PROTECT AF trials showed, the left atrial appendage closure was noninferior to systemic anticoagulation with warfarin [26]. Vivek et al. reported that after 3.8 ± 1.7 years of follow-up among patients with nonvalvular AF at high risk for stroke, percutaneous left atrial appendage closure, compared with warfarin anticoagulation therapy, met criteria for both non-inferiority and superiority [27]. However, the current large-scale clinical trials

are limited to the comparison between Watchman and warfarin. The comparison between other implantable devices and warfarin, and the comparison between implantable devices and NOACs still need to be validated.

Existing Problems and Prospects

The current guidelines recommend application of bleeding risk score is HAS-BLED score (including hypertension, abnormal liver/renal function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol). A recent clinical trial showed, among HAS-BLED, ORBIT (including old age, reduced hemoglobin/hematocrit/anemia, bleeding history, insufficient kidney function, treatment with platelets), ATRIA (anticoagulation and risk factors in AF) and HEMORR2HAGES (hepatic or renal disease, ethanol abuse, malignancy history, age>75, reduced platelet count or function, rebleeding risk, hypertension, anemia, genetic factors, excessive fall risk, stroke history) scores, the ORBIT score presented the best discrimination and calibration [28]. The bleeding score will continue to update follow up with the results of large-scale clinical trials, which helps clinical doctors to avoid exaggerating the risk of bleeding, and the patients to benefit more [29,30]. More and more clinical studies showed, cryoballoon ablation had the advantages of short operation time, operation technology is relatively easy to grasp, high success rate and low main complication rates [31]. And it is believed that after the clinical use of third-generations of cryoballoon, the cryoablation will have a better prospect.

However, in addition to focusing on "ice and fire", we need further understand the mechanism of incidence and maintenance of AF. At present, the main pathophysiological mechanisms of AF include atrial structure remodeling, autonomic remodeling, electrical remodeling, role of rotors and complex fractionated electrograms [13]. We may have omitted something about the mechanism of AF. A thorough understanding of the mechanism of AF allows us to manage AF better [32]. Some researchers tried to evaluate the role of gastrointestinal disorders in the genesis of arrhythmias such as atrial fibrillation. So we use PPI after RFCA as a common therapy, especially in patients with comorbidities of gastro esophageal reflux disease [33].

Conclusion

AF is not only a huge challenge, but also an impetus for us.

With more and more new drugs into clinical use and the continuous improvement of operation method, the success rate of AF will be increased. The quality of life of patients will be improved, the social and economic burden will be reduced.

References

- Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, et al. (2014) Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. *Circulation* 129: 837-847.
- Colilla S, Crow A, Petkun W, Singer DE, Simon T, et al. (2013) Estimates of current and future incidence and prevalence of AF in the US adult population. *The American Journal of Cardiology* 112: 1142-1147.
- Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, et al. (2013) Projections on the number of individuals with AF in the European union from 2000 to 2060. *European Heart Journal* 34: 2746-2751.
- Zoni-Berisso M, Lercari F, Carazza T (2014) Epidemiology of AF: European perspective. *Clinical Epidemiology* 6: 213-220.
- Frost JL, Campos-Outcalt D, Hoelting D, LeFevre M, Lin KW, et al. (2017) Atrial fibrillation guideline summary. *Annals Family Medicine* 15: 490-491.
- Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, et al. (2011) Rivaroxaban versus warfarin in nonvalvular AF. *New England Journal of Medicine* 365: 883-891.
- Granger CB, Alexander JH, Lopes RD, Hylek EM, McMurray JJ, et al. (2011) Apixaban versus warfarin in patients with AF. *New England Journal of Medicine* 365: 981-992.
- Wang K, Li H, Kwong WJ, Antman EM, Ruff CT, et al. (2017) Impact of Spontaneous Extracranial Bleeding Events on Health State Utility in Patients with AF: Results from the ENGAGE AF-TIMI 48 Trial. *Journal of the American Heart Association* 6: e006703.
- Haft JI (2014) Edoxaban versus warfarin for venous thromboembolism. *New England Journal of Medicine* 370: 80-81.
- Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, et al. (2009) Dabigatran versus warfarin in patients with AF. *New England Journal of Medicine* 361: 1139-1151.
- Rajagopalan B, Curtis AB (2015) Management of AF: What is new in the 2014 ACC/AHA/HRS guideline?. *Postgraduate Medicine* 127: 396-404.
- Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, et al. (2017) 2016 ESC Guidelines for the Management of AF Developed in Collaboration With EACTS. *Revista Espanola Cardiologia* 70: 50.
- Maron BJ, Gohman TE, Kyle SB, Estes NAM, Link MS (2002) Clinical profile and spectrum of commotio cordis. *JAMA* 287: 1142-1146.
- Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, et al. (2015) Approaches to catheter ablation for persistent AF. *New England Journal of Medicine* 372: 1812-1822.
- Mody BP, Raza A, Jacobson J, Iwai S, Frenkel D, et al. (2017) Ablation of long-standing persistent AF. *Annals of Translational Medicine* 5: 305.
- Andrade JG, Dubuc M, Guerra PG, Macle L, Rivard L, et al. (2012) Cryoballoon ablation for AF. *Indian Pacing and Electrophysiology Journal* 12: 39-53.
- Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne J, et al. (2013) Cryoballoon ablation of pulmonary veins for paroxysmal AF: first results of the North American Arctic Front (STOP AF) pivotal trial. *Journal of American of Cardiology* 61: 1713-1723.
- Tzeis S, Pastromas S, Sikiotis A, Andrikopoulos G (2016) Cryoablation in persistent AF - a critical appraisal. *Netherlands Heart Journal* 24: 498-507.
- Ciconte G, Ottaviano L, De Asmundis C, Baltogiannis G, Conte G, et al. (2015) Pulmonary vein isolation as index procedure for persistent AF: One-year clinical outcome after ablation using the second-generation cryoballoon. *Heart Rhythm* 12: 60-66.
- Lemes C, Wissner E, Lin T, Mathew S, Deiss S, et al. (2016) One-year clinical outcome after pulmonary vein isolation in persistent AF using the second-generation 28 mm cryoballoon: a retrospective analysis. *Europace* 18: 201-205.
- Ciconte G, Baltogiannis G, De Asmundis C, Sieira J, Conte G, et al. (2015) Circumferential pulmonary vein isolation as index procedure for persistent AF: a comparison between RFCA and second-generation cryoballoon ablation. *Europace* 17: 559-565.
- Kenigsberg DN, Martin N, Lim HW, Kowalski M, Ellenbogen KA (2015) Quantification of the cryoablation zone demarcated by pre- and postprocedural electroanatomic mapping in patients with AF using the 28-mm second-generation cryoballoon. *Heart Rhythm* 12: 283-290.
- Narayan SM, Baykaner T, Clopton P, Schricker A, Lalani GG, et al. (2014) Ablation of rotor and focal sources reduces late recurrence of AF compared with trigger ablation alone: extended follow-up of the CONFIRM trial (Conventional Ablation for AF With or Without Focal Impulse and Rotor Modulation). *Journal of American College Cardiology* 63: 1761-1768.
- Baykaner T, Lalani GG, Schricker A, Krummen DE, Narayan SM (2014) Mapping and ablating stable sources for AF: summary of the literature on Focal Impulse and Rotor Modulation (FIRM). *J Interv Card Electrophysiol* 40: 237-244.
- Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, et al. (2012) 2012 focused update of the ESC Guidelines for the management of AF: an update of the 2010 ESC Guidelines for the management of AF developed with the special contribution of the European Heart Rhythm Association. *European Heart Journal* 33: 2719-2747.
- Reddy VY, Doshi SK, Sievert H, Buchbinder M, Neuzil P, et al. (2013) Percutaneous left atrial appendage closure for stroke prophylaxis in patients with AF. *Circulation* 127: 720-729.
- Reddy VY, Sievert H, Halperin J, Doshi SK, Buchbinder M, et al. (2014) Percutaneous left atrial appendage closure vs warfarin for AF: a randomized clinical trial. *JAMA* 312: 1988-1998.
- Proietti M, Hijazi Z, Andersson U, Connolly SJ, Eikelboom JW, et al. (2017) Comparison of Bleeding Risk Scores in Patients with AF: Insights from the RE-LY Trial. *J Intern Med*.
- Bungard TJ, Ghali WA, Teo KK, McAlister FA, Tsuyuki RT, et al. (2000) Why do patients with AF not receive warfarin?. *Arch Intern Med* 160: 41-46.
- Steinberg BA, Shrader P, Thomas L, Ansell J, Fonarow GC, et al. (2016) Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes: The ORBIT-AF II Registry. *J Am Coll Cardiol* 68: 2597-2604.
- Liu XH, Chen CF, Gao XF, Xu YZ (2016) Safety and Efficacy of Different Catheter Ablations for AF: A Systematic Review and Meta-Analysis. *Pacing and Clinical Electrophysiology* 39: 883-899.
- Sayed M, El Maghawry M (2016) FIRE AND ICE: The quest for the perfect modality in AF ablation. *Glob Cardiol Sci Pract* 2016: e201623.
- Gesualdo M, Scicchitano P, Carbonara S, Ricci G, Principi M, et al. (2016) The association between cardiac and gastrointestinal disorders: causal or casual link? *Journal of Cardiovascular Medicine* 17: 330-338.