Management of atrial fibrillation
Pasquale Vergara* and Paolo Della Bella

Address: Arrhythmia Unit and Electrophysiology Laboratories, Department of Cardiology and Cardiothoracic Surgery, Ospedale S. Raffaele, via Olgettina 60, Milano, Italy
* Corresponding author: Pasquale Vergara (pasqualevergara@yahoo.it)

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 CHA2DS2-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 CHADS2 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 reconnection across PV isolation; Nanthakumar et al. [40] found reconnection 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 atrial 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.

References
1. Benjamin EJ, Levy D, Vaziri SM, D’Agostino RB, Belanger AJ, Wolf PA: Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA 1994, 271:840-44.
2. Kannel WB, Abbott RD, Savage DD, McNamara PM: Epidemiologic features of chronic atrial fibrillation: the Framingham study. N Engl J Med 1982, 306:1018-22.
3. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D’Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ: Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation 2004, 110:1042-46.
4. Hart RG, Pearce LA, Aguilar MI: Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007, 146:857-67.
5. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P. Guidelines ESCCfP: 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012, 33:2719-47.
6. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ: Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Qost 2010, 137:263-72.
7. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY: A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Qost 2010, 138:1093-100.
8. Watson T, Shantsila E, Lip GY: Mechanisms of thrombogenesis in atrial fibrillation: Virchow’s triad revisited. Lancet 2009, 373:155-66.
9. Mant J, Hobbs FD, Fletcher K, Roalle A, Fitzmaurice D, Lip GY, Murray E, investigators B, Midland Research Practices N: Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet 2007, 370:493-503.
10. Investigators AWWGotA, Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, Yusuf S: Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet 2006, 367:1903-12.
11. Investigators A, Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, Chrolavicius S, Yusuf S: Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med 2009, 360:2066-78.
12. Connolly SJ, Ezekowitz MD, Yusuf S, Ezekowitz MD, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener H, Joyner CD, Wallentin L: Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2011, 364:1139-51.
13. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Baht MC, Diaz R, Easton JD, Ezekowitz JA, Fiesler C, Garcia D, Geraldes M, Gersh BJ, Gollin S, Goto S, Homma JL, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JI, Pai P, Parkhomenko A,
Verheugt FWA, et al.: *Apixaban versus warfarin in patients with atrial fibrillation*. *N Engl J Med* 2011, 365:981-92.

14. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JJ, Spinar J, Ruzyllo W, Ruda M, Kasukune Y, Bechler J, Shi M, G rip LT, Patel SP, Patel I, Hansyok J, Mercuri M, Antman EM: *Edoxaban versus warfarin in patients with atrial fibrillation*. *N Engl J Med* 2013, 369:2093-104.

15. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JJ, Lewis BS, Parkhomenko A, Yamashita T, Antman EM: *Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials*. *Lancet* 2013.

16. Hohnloser SH, Kuck KH, Lilienhal J: *Rhythm or rate control in atrial fibrillation—Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial*. *Lancet* 2000, 356:1789-94.

17. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Michel MC, Dalquist JE, Corley SD: *A comparison of rate control and rhythm control in patients with atrial fibrillation*. *N Engl J Med* 2002, 347:1825-33.

18. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, Said SA, Darmanata JI, Timmermans AJ, Tijssen JG, Crijns HJ: *A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation*. *N Engl J Med* 2002, 347:1834-40.

19. Carlsson J, Mietic S, Windeler J, Cuneo A, Haun S, Micus S, Walter S, Tebbe U: *Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study*. *J Am Coll Cardiol* 2003, 41:1690-96.

20. Caldeira D, David C, Sampaio C: *Rate vs rhythm control in patients with atrial fibrillation and heart failure: a systematic review and meta-analysis of randomised controlled trials*. *Eur J Intern Med* 2011, 22:448-55.

21. Roy D, Talajic M, Nastel S, Wyse DG, Dorian P, Lee KL, Bourassa MG, Arnold JMO, Buxton AE, Camm AJ, Connolly SJ, Deenadayalu N, Lennon LW, Lewis BS, Parkhomenko A, Yamashita T, Antman EM: *Comparison of sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study*. *Circulation* 2004, 109:1509-13.

22. Corley SD, Epstein AE, DiMarco JP, Domanski MJ, Geller N, Greene HL, Josephson RA, Kellen JC, Klein RC, Krahn AD, Michiel M, Mitchell LB, Nelson JD, Rosenberg Y, Schron E, Shenanski L, Waldo AL, Wyse DG: *Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study*. *Circulation* 2004, 109:1509-13.

23. Wilber DJ, Pappone C, Neuzil P, de Paola A, Marchlinski F, Natale A, Madle L, Daoudd EG, Calkins H, Hall B, Reddy V, Augello G, Reynolds MR, Vinekar C, Liu CY, Berry SM, Barry DA: *Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial*. *JAMA* 2010, 303:333-40.

24. Chang S, Tai C, Lin Y, Wongcharoen W, Lo L, Tuan T, Udyaar AR, Chang S, Tsao H, Hsieh M, Hu Y, Chen Y, Chen S: *Biatrial substrate properties in patients with atrial fibrillation*. *J Cardiovasc Electrophysiol* 2007, 18:134-9.

25. Oakes RS, Badger TJ, Kholsmeski EG, Akoun M, Burgen NS, Fish EN, Blauer JJ, Rao SN, DiBella EVR, Segerson NM, Daccarett M, Windfelder J, Pacifici C, Parker D, MacLeod RS, Marrouche NF: *Dual ablation and quantification of left atrial structural remodeling with delayed-enhancement magnetic resonance imaging in patients with atrial fibrillation*. *Circulation* 2009, 119:1758-67.

26. Pappone C, Rosano S, Augello G, Gallus G, Vicedomini G, Mazzone P, Gulletta S, Gugliotta F, Pappone A, Santinelli V, Tortorillo V, Sala S, Zangrillo A, Cresti G, Benussi S, Alferi O: *Mortality, morbidity, and quality of life after circumferential pulmonary vein ablation for atrial fibrillation: outcomes from a controlled nonrandomized long-term study*. *J Am Coll Cardiol* 2003, 42:85-97.

27. Gaita F, Caponi D, Scaglione M, Montefusco A, Corleto A, Di Monte F, Coin D, Di Donna P, Giustetto C: *Long-term clinical results of 2 different ablation strategies in patients with paroxysmal and persistent atrial fibrillation*. *Circ Arrhythm Electrophysiol* 2008, 1:269-75.

28. Sawhney N, Anousheh R, Chen WC, Narayan S, Feld GK: *Five-year outcomes after segmental pulmonary vein isolation for paroxysmal atrial fibrillation*. *Am J Cardiol* 2009, 104:366-72.

29. Bhargava M, Di Biase L, Mohany P, Prasad S, Martin DO, Williams-Andrews M, Wazni OM, Burkhardt JD, Cummings JE, Khaykin Y, Verma A, Hao S, Beheiry S, Hongo R, Rosillo A, Raviele A, Bonso A, Themistochiakis S, Stewart K, Saliba V, Schweikert RA, Natale A: *Impact of type of atrial ablation and repeat catheter ablation on long-term freedom from atrial fibrillation: results from a multicenter study*. *Heart Rhythm* 2009, 6:1403-12.

30. Tzou WS, Marchlinski FE, Zado ES, Lin D, Dijkstra C, Cooper MM, Bala R, Garcia A, Hutchinson MD, Riley MP, Verdon R, Gerstenfeld EP: *Long-term outcome after successful catheter ablation of atrial fibrillation*. *Circ Arrhythm Electrophysiol* 2010, 3:237-42.

31. Ouyang F, Tilz R, Chun J, Schmidt B, Wiessner E, Zerr T, Neven K, Kokert B, Konstantindou M, Mezzner A, Fuenkranz A, Kuck K: *Long-term results of catheter ablation in paroxysmal atrial fibrillation: lessons from a 5-year follow-up*. *Circulation* 2010, 122:2368-77.

32. Medei C, Sparks PB, Morton JB, Kistler PM, Halloran K, Rosso R, Vohra JK, Kumar S, Kalman JM: *Pulmonary vein antral isolation for paroxysmal atrial fibrillation: results from long-term follow-up*. *J Cardiovasc Electrophysiol* 2011, 22:137-41.

33. Weerasooriya R, Khairy P, Lilarten J, Madle L, Hocini M, Sacher F, Lellouche N, Knecht S, Wright M, Naiu I, Miyazaki S, Scavee C, Clementy J, Haissaguerre M, Jais P: *Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up?*. *J Am Coll Cardiol* 2011, 57:160-66.

34. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Moureau A, Le Metayer P, Clementy J: *Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins*. *N Engl J Med* 1998, 339:659-66.

35. Chen SA, Hsieh MH, Tai CT, Tsai CF, Prakashe VS, Yu WC, Hsu TL, Ding YA, Chang MG: *Initiation of atrial fibrillation by ectopic beats originating from the pulmonary veins: electrophysiological characteristics, pharmacological responses, and effects of radiofrequency ablation*. *Circulation* 1999, 100:1879-86.

36. Pappone C, Oreno G, Rosano S, Vicedomini G, Tocchi M, Gugliotta F, Salvati A, Cicinale D, Calabrò MP, Mazzione P, Ficarra E, Di Gioia C, Gulletta S, Santiellini V, Benussi S, Alfieri O: *Atrial electroanatomical remodeling after circumferential radiofrequency pulmonary vein ablation: efficacy of an anatomic approach in a large cohort of patients with atrial fibrillation*. *Circulation* 2001, 104:2539-44.

37. Oral H, Knight BP, Tada H, Ozaydin M, Chugh A, Hassan S, Scharf C, Lai SWK, Greenstein R, Pelosi F, Strickberger SA, Morady F: *Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation*. *Circulation* 2002, 105:1077-81.
38. Ouyang F, Bansch D, Ernst S, Schaumann A, Hachiya H, Chen M, Chun J, Falk P, Khanezadi A, Antz M, Kuck KH: Complete isolation of left atrium surrounding the pulmonary veins: new insights from the double-Lasso technique in paroxysmal atrial fibrillation. Circulation 2004, 110:2090-29.

39. Ganesan AN, Shipp NJ, Brooks AG, Kuklik P, Lau DH, Lim HS, Sullivan T, Roberts-Thomson KC, Sanders P: Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. J Am Heart Assoc 2013, 2:e004549.

40. Nanthakumar K, Plumb VJ, Epstein AE, Veenhuyzen GD, Link D, Kay GN: Resumption of electrical conduction in previously isolated pulmonary veins: rationale for a different strategy? Circulation 2004, 109:1226-29.

41. Verma A, Kilicaslan F, Pisano E, Marrouche NF, Fanelli R, Brachmann J, Geunther J, Potenza D, Martin DO, Cummings J, Burkhardt JD, Saliba W, Schweikert RA, Natale A: Response of atrial fibrillation to pulmonary vein antrum isolation is directly related to resumption and delay of pulmonary vein conduction. Circulation 2005, 112:2627-35.

42. Kuck K, Reddy YY, Schmidt B, Natale A, Neuzil P, Kautzner J, Herrera C, Hindricks G, Jais P, Nakagawa H, Lambert H, Shah DC: A novel radiofrequency ablation catheter using contact force sensing: Toccata study. Heart Rhythm 2012, 9:18-23.

43. Reddy YY, Shah D, Kautzner J, Schmidt B, Saoudi N, Herrera C, Jais P, Hindricks G, Peichl P, Yuzbasi A, Lambert H, Neuzil P, Natale A, Kuck K: The relationship between contact force and clinical outcome during radiofrequency catheter ablation of atrial fibrillation in the TOCCATA study. Heart Rhythm 2012, 9:1789-95.

44. Boersma LV, Wijffels MC, Oral H, Wever EF, Morady F: Pulmonary vein isolation by duty-cycled bipolar and unipolar radiofrequency energy with a multielectrode ablation catheter. Heart Rhythm 2008, 5:1635-42.

45. Wieczorek M, Høelgen R, Akin E, Salili AR, Oral H, Morady F: Results of short-term and long-term pulmonary vein isolation for paroxysmal atrial fibrillation using duty-cycled bipolar and unipolar radiofrequency energy. J Cardiovasc Electrophysiol 2010, 21:399-405.

46. Van Belle Y, Janse P, Rivera-Ayerza MJ, Thornton AS, Jessurun ER, Theuns D, Jordaes L: Pulmonary vein isolation using an occluding cryoballoon for circumferential ablation: feasibility, complications, and short-term outcome. Eur Heart J 2007, 28:2321-37.

47. Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG, Dubuc M, Reddy V, Nelson L, Holcombe RG, Lehmann JW, Ruskin JN: Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. J Am Coll Cardiol 2013, 61:1713-23.

48. Dukkipati SR, Kuck K, Neuzil P, Woollert I, Kautzner J, McElderry HT, Schmidt B, Gerstenfeld EP, Doshi SK, Horton R, Metzner A, d’Avila A, Ruskin JN, Natale A, Reddy YY: Pulmonary vein isolation using a visually guided laser balloon catheter: the first 200 patient multicenter clinical experience. Circ Arrhythm Electrophysiol 2013, 6:467-72.

49. Børgdøgn S, Chui KR, Gunawardene M, Fuenkranz A, Urban V, Schulte-Hahn B, Nowak B, Schmidt B: Comparison of balloon catheter ablation technologies for pulmonary vein isolation: the laser versus cryo study. J Cardiovasc Electrophysiol 2013, 24:987-94.

50. Wijffels MC, Kirchhof C, Dorland R, Allessie MA: Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation 1995, 92:1954-68.

51. Hocini M, Jais P, Sanders P, Takahashi Y, Rotter M, Rostock T, Hsu LF, Sacher F, Reuter S, Clementy J, Haissaguerre M: Techniques, evaluation, and consequences of linear block at the left atrial roof in paroxysmal atrial fibrillation: a prospective randomized study. Circulation 2005, 112:3688-96.

52. Jais P, Hocini M, Hsu L, Sanders P, Savec C, Weerasooriya R, Macle L, Raybaud F, Garrigue S, Shah DC, Le Metayer P, Clementy J, Haissaguerre M: Technique and results of linear ablation at the mitral isthmus. Circulation 2004, 110:2996-3002.

53. Chae S, Oral H, Good E, Dey S, Wimmer A, Crawford T, Wells D, Sarrazin J, Chalfoun N, Kuhne M, Fortino J, Huetter E, Lemerand T, Pelosi F, Bogun F, Morady F, Chugh A: Atrial tachycardia after circumferential pulmonary vein ablation of atrial fibrillation: mechanistic insights, results of catheter ablation, and risk factors for recurrence. J Am Coll Cardiol 2007, 50:1781-7.

54. Jais P, Hocini M, O’Neill MD, Klein GJ, Knecht S, Sheirom M, Arentes L, Kodali S, Clementy J, Haissaguerre M: How to perform linear lesions. Heart Rhythm 2007, 4:803-9.

55. Nademanee K, McKenzie J, Kosar E, Schwab M, Sunaneevisitayakul B, Vasavakul T, Khunnawat C, Ngarmukos T: A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. J Am Coll Cardiol 2004, 43:2044-53.

56. Dixit S, Marchlinski FE, Lin D, Callans DJ, Bala R, Riley MP, Garcia FC, Hutchinson MD, Racicliffe SJ, Cooper JM, Verdelo R, Patel YV, Zado ES, Cash NR, Killian T, Tomson TT, Gerstenfeld EP: Randomized ablation strategies for the treatment of persistent atrial fibrillation: RASTA study. Circ Arrhythm Electrophysiol 2012, 5:287-94.

57. Narayan SM, Krummen DE, Rappel WJ: Clinical mapping approach to diagnose electrical rotors and focal impulse sources for human atrial fibrillation. J Cardiovasc Electrophysiol 2012, 23:447-54.

58. Narayan SM, Krummen DE, Clopton P, Shivkumar K, Miller JM: Direct or coincidental elimination of stable rotors or focal sources may explain successful atrial fibrillation ablation: on-treatment analysis of the CONFIRM trial (Conventional Ablation for AF with or without focal impulse and rotor modulation). J Am Coll Cardiol 2013, 62:38-47.

59. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM: Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial. J Am Coll Cardiol 2012, 60:528-36.