

Knots to untie: anticoagulant and antiarrhythmic therapy after ablation for atrial fibrillation

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The continuation or otherwise of anticoagulant and antiarrhythmic therapy after ablation of atrial fibrillation (AF) is one of the main aspects still to be defined in the electrophysiological field. The currently available data do not allow the assumption of certain positions due to the lack of randomized studies on the subject. With regard to anticoagulant therapy, however, the suggestion of the guidelines to assess more the risk profile than the result of the ablation and consequently to prescribe anticoagulant treatment to all patients with CHADSVASc ≥ 2 seems acceptable. Its use in the first two or three months after the procedure appears reasonable; however, keeping in mind that the objective of this strategy is limited to the prevention of early recurrences only. More prolonged use of antiarrhythmics seems to be more promising, but further data are necessary before it can be recommended routinely. The ablation of AF is a therapy that is widely spreading and its use is continuously growing. Since it is a recently introduced method, not everything is still clear about it. The continuation or not of anticoagulant and antiarrhythmic therapy after ablation for AF is one of the main aspects yet to be defined.

Anticoagulant therapy

Atrial fibrillation (AF) is an important cause of cerebral thromboembolic episodes. It is estimated that at least 15% of the strokes is attributable to this arrhythmia and, furthermore, it is hypothesized that unknown forms of AF may be responsible for a share, still to be determined but certainly not negligible, of that 25% of ischaemic strokes that remain without evident cause. In the context of patients with AF, anticoagulant therapy has amply demonstrated its effectiveness by reducing the risk of stroke by 64% and that of death by 25%.¹ However, in studies with subjects subjected to ablation for AF, several studies report a particularly low thromboembolic risk and not further modified by the chronic administration of anticoagulants, which, on the contrary, induce an increase in the bleeding risk.² These reports therefore raised doubts about the effective opportunity of continuing the anticoagulant therapy after performing a successful ablation. At the moment, the data

available in the literature do not unfortunately allow to definitively resolve the issue. For a summation of causes (manipulation of the atrium, scars, inflammatory state, etc.), thromboembolic episodes are more frequent in the first three months after the procedure, and therefore the only certainty currently available is that in this time span all subjects must undergo anticoagulation. At the end of this period, the guidelines suggest whether or not to continue the anticoagulant therapy based on the basic thromboembolic risk and not the result of the ablation and therefore to treat with anticoagulant therapy all subjects with a CHADSVASc ≥ 2 . In reality, we proceed, on the other hand, in a non-uniform way, as demonstrated for example by a Danish Register³ which shows that, after 5 years from the procedure, about 40% of the subjects with CHADSVASc = 0, and therefore without indication to the anticoagulant, were still with this therapy, while 30% of those with CHADSVASc ≥ 2 , therefore in need according to the anticoagulant guidelines, had instead suspended it. Certainly, these data are affected by the lesson of AFFIRM,⁴ the first major study of comparison between a strategy of rhythm control and that of frequency control, in which rhythm-

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control did not induce a significant reduction in strokes, probably due to the early suspension of anticoagulant therapy in these patients. Unjustified suspension also in light of the obvious consideration that rhythm control is an antiarrhythmic and not an anti-stroke therapy. On the other hand, ablation is nothing more than a form, albeit sophisticated and more effective, of rhythm control. Therefore, if in patients subjected to rhythm control with drugs it is unanimously based on CHADSVASc to decide on anticoagulant therapy it is not clear why one should behave differently after ablation, at least until it is clearly demonstrated that this procedure is actually able to modify the natural history of AF. The CHADSVASc algorithm has also confirmed its prognostic capacity, even in subjects treated with ablation,⁵ in which it is able to predict, in addition to the thromboembolic risk, also the probability of arrhythmic recurrence, hospitalization for heart failure, or death. Another aspect to remember is that the ablation is however burdened, depending on the length of the follow-up, by a high percentage of relapses⁶ and that, after the procedure, the asymptomatic episodes of AF increase (with a ratio towards the symptomatic ones which goes from 1.1 to 3.7), which are also shorter (certainly positive for the patient but which makes these events more difficult to detect). For these reasons, therefore, trusting the apparent success of the procedure can be misleading. In interpreting then the contradiction provided by the literature data, on the limited usefulness of anticoagulant therapy after ablation, it must be taken into account that none of these studies was randomized, that the patients included were mostly young, that the case studies were small while the low rate of thromboembolic events would have required large numbers, that the majority of the data was obtained with the use of Warfarin and therefore cannot be automatically extrapolated to NAO, and that many of the patients included in the studies had a low thromboembolic risk, that the follow-ups were short, that there were no data on silent cerebral events and cognitive impairment, that, still, the subjects who stopped the anticoagulant therapy often alternatively took aspirin, that the suspension of the anticoagulant therapy occurred in heterogeneous times (3-6-12 months after the procedure) and that, in case of recurrence of AF, anticoagulant therapy was resumed. The analysis of these data therefore shows that the thromboembolic risk after ablation, in the patients included in these studies, is certainly low, however, it raises the doubt whether the patients with AF subjected to ablation are the same patients as those treated in another way. That is, if the low thromboembolic risk observed after ablation depends on the actual benefits of the procedure or if instead the healthiest patients are 'ablated' and therefore for this reason they have a lower thromboembolic risk.

In the absence of randomized studies on the topic, which are also ongoing, numerous meta-analyses have been produced which have provided conflicting results such as those of Proietti *et al.*⁷ and Romero *et al.*⁸ In the first, anticoagulant therapy was not effective unlike what was shown in the second. A possible explanation of this dissonance is probably to be found in the different basic thromboembolic risk profile of the patients included in the analysis. In the

first 90% of patients had a CHADSVASc of 0 or 1, in the second almost 50% of the subjects had a CHADSVASc ≥ 2 .

Another element to be taken into consideration is the distant temporal relationship between AF episodes and thromboembolic events, highlighted by studies⁹ in carriers of intracardiac devices (pacemakers, loop recorders, and defibrillators), which challenged the paradigm of classic AF as a cause of stroke and has given rise to the suspicion that this arrhythmia is actually more of a further marker of thromboembolic risk. In this case, the elimination of AF by ablation, even if actually successful, would not in any case justify the suspension of the anticoagulant, since arrhythmia is not the only cause of the increased incidence of thromboembolism.

In conclusion, pending the ongoing randomized studies, the proposal of the guidelines to assess more the risk profile than the result of the ablation certainly appears reasonable. With this in mind, anticoagulant therapy should be prescribed to patients with CHADSVASc ≥ 2 and suspended to those with CHADSVASc = 0. In patients with, instead, CHADSVASc = 1, the decision should be made individually considering in addition to the thromboembolic risk also the haemorrhagic risk, as well as additional parameters such as the those of the CHADSVASc algorithm present (the 'specific weight' is not the same for everyone), kidney function, body weight, type of AF (paroxysmal vs. persistent/permanent), atrial size, auricle flow velocity, and its morphology.

Antiarrhythmic therapy

The ablation of AF is burdened by a non-negligible rate of recurrence, 50-60% after 5 years, with an annual rate of 10%.¹⁰ These are divided into early (in the first 3 months) and late (from the third month onwards). The mechanisms of the two different types of recurrence are different. Early relapses are affected by transient phenomena such as (i) acute inflammation caused by the ablation procedure, (ii) the early resumption of electrical activity in the ablation site lines, (iii) a temporary imbalance of the autonomic nervous system, and (iv) a delayed lesion formation. Late relapses are mainly promoted by the recovery of conduction between the pulmonary veins and the atrium. Early relapses, although not an indication of procedure failure, however, significantly increase the probability of late ones. In common clinical practice, antiarrhythmic drugs are usually used after ablation, especially in non-paroxysmal forms. For example, the data from the ESC-EHRA register show that 45% of patients are on antiarrhythmic therapy 1 year after the procedure and that, subsequently, this percentage drops only slightly, reaching around 35%.¹¹ Often antiarrhythmic therapy is used for a short period, generally 3 months, with the aim of preventing early recurrences, which, although are not an expression of ablative failure, they are still a source of psychological distress for the patient and cause an increased use of resources for hospitalizations and cardioversions. The cycle of antiarrhythmic therapy is also administered in the hypothesis that maintenance of sinus rhythm in the first months after the procedure may favour

the process of ‘inverse remodelling’ of the atrium and therefore induce a reduction also in late recurrences. In other cases, antiarrhythmic therapy is continued over the long term in the hope of improving the success of the ablation. The data available in the literature are limited and therefore the real effectiveness of maintaining antiarrhythmic drugs after ablation is still a hot topic.

Results of short-term administration of antiarrhythmic therapy

Five randomized trials investigated the topic. The 5A Study¹² took 6 weeks of antiarrhythmic therapy (which did not include amiodarone) and observed no difference in relapses at 6 months. AMIO-CAT¹³ instead used 8 weeks of amiodarone and found a significant reduction in recurrence at 3 months but no difference at 6 months. In Gu’s study¹⁴ 2 months of therapy decreased AF reappearances at 60 days but had no effect after 1 year. Hayashi *et al.*,¹⁵ on the other hand, with 3 months of therapy with flecainide did not report any positive effects on early or late relapses. Finally, EAST-AF,¹⁶ the largest of these studies with its 2038 patients enrolled and who used three months of antiarrhythmic therapy, confirmed the 90-day recurrence reduction effect and the lack of efficacy, instead, after a year. The various meta-analyses¹⁷⁻²⁰ conducted have all confirmed the effectiveness of a short cycle of antiarrhythmic therapy in preventing early relapses and its lack of effect on late relapses. The only discordant voice is the non-randomized study of Kettering²¹ in which 3 months of amiodarone reduced relapses to both 3 and 24 months (even if they had no effect 12 months after the procedure).

The set of data therefore leads us to conclude that a short cycle of antiarrhythmic therapy after ablation is reasonable to reduce the probability of unpleasant early recurrences of the arrhythmia but that this conduct is not able to influence the subsequent outcome. This is explained by the prevailing mechanism of late recurrences, that is, the resumption of conduction between the pulmonary veins and the atrium, an event which, a short cycle of antiarrhythmic therapy, also with its possible beneficial effects on the ‘inverse remodelling’ of the atrium, it is incapable of affecting.

Results of protracted antiarrhythmic therapy

Much scarcer are the data on the effectiveness of the long-term continuation of antiarrhythmic drugs after ablation. In fact, we have only two studies, one of which, the POWDER AF,²² randomized and the other, that of Mesquita,¹⁰ retrospective. In the first 153 patients with paroxysmal AF were subjected to ablation and treated for 3 months with antiarrhythmic drugs. At the end of this period, those who remained without relapses were randomized to continue the therapy for 1 year or less. At the end of the 12 months of follow-up, antiarrhythmic therapy significantly reduced relapses (2.7% vs. 21.9%, $P < 0.001$). A similar result was produced by the other study in which 55% of the 144 subjects included was on antiarrhythmic therapy

12 months after ablation and had a significantly greater success rate of the procedure (86% vs. 76%, $P < 0.001$).

The positive effect of the therapy shown by POWDER AF seems independent of the action on atrial remodelling and is instead expressed through three distinct mechanisms. (i) After the ablative procedure it is not uncommon, to observe a partial resumption of conduction between the atrium and pulmonary veins that can be counteracted by drug therapy, (ii) not all the triggers of AF derive from the pulmonary veins for which the drugs can suppress the effect of these, as well as, other residual triggers, (iii) by influencing the electrophysiological properties of the atrial substrate, therapy can reduce the probability that a trigger will be able to initiate an episode of AF.

The POWDER AF data, although intriguing, need further confirmation also for the smallness of the sample studied. Nonetheless, the prolonged use of antiarrhythmic therapy after ablation can be reasonable, as it can contribute at least to that improvement in symptoms which at the moment still remains the main indication for ablation. In fact, only a minority of patients approach this procedure with the aim of freeing themselves from drug therapy. Other data supporting the continued use of antiarrhythmic drugs comes from a recent work²³ on about 3600 patients who underwent ablation and were followed for about 6 years, in which the mortality of 62% for those taking antiarrhythmic drugs was not increased compared to those for whom the drugs were not prescribed, even presenting a trend of reduction of the same which, although not statistically significant, seems to dispel the doubts about the lack of safety of this therapy.

Conclusions

The continuation or otherwise of anticoagulant and antiarrhythmic therapy after ablation of AF is one of the main aspects still to be defined in the electrophysiological field. The currently available data do not allow the assumption of firm positions. Regarding anticoagulant therapy, however, the suggestion of the guidelines to assess more the risk profile than the result of the ablation and consequently to anticoagulate all patients with CHADSVASc ≥ 2 seems acceptable. Its use in the first two or three months after the procedure appears reasonable; however, keeping in mind that the objective of this strategy is limited to the prevention of early recurrences only. More prolonged use of antiarrhythmics seems to be more promising, but further data are necessary before it can be recommended routinely.

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References

- Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent strokes in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;146:857-867.
- Themistoclakis S, Corrado A, Marchlinski FE, Jais P, Zado E, Rossillo A, Di Biase L, Schweikert RA, Saliba WJ, Horton R, Mohanty P, Patel D, Burkhardt DJ, Wazni OM, Bonso A, Callans DJ, Haissaguerre M, Raviele A, Natale A. The risk of thromboembolism and need for oral anticoagulation after successful atrial fibrillation ablation. *J Am Coll Cardiol* 2010;55:735-743.

3. Karasoy D, Gislason GH, Hansen J, Johannessen A, Køber L, Hvidtfeldt M, Özcan C, Torp-Pedersen C, Hansen ML. Oral anticoagulation therapy after radiofrequency ablation of atrial fibrillation and the risk of thromboembolism and serious bleeding: long-term follow-up in nationwide cohort of Denmark. *Eur Heart J* 2015;**36**:307-314.
4. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;**347**:1825-1833.
5. Jacobs V, May HT, Bair TL, Crandall BG, Cutler M, Day JD, Weiss JP, Osborn JS, Muhlestein JB, Anderson JL, Mallender C, Bunch TJ. The impact of risk score (CHA₂DS₂-VAS_c) on long-term outcomes after atrial fibrillation ablation. *Heart Rhythm* 2015;**12**:681-686.
6. Chao T-F, Lin Y-J, Chang S-L, Lo L-W, Hu Y-F, Chung F-P, Liao J-N, Chen S-A. Can oral anticoagulants be stopped safely after a successful atrial fibrillation ablation? *J Thorac Dis* 2015;**7**:172-177.
7. Proietti R, AlTurki A, Di Biase L, China P, Forleo G, Corrado A, Marras E, Natale A, Themistoclakis S. Anticoagulation after catheter ablation of atrial fibrillation: an unnecessary evil? A systematic review and meta-analysis. *J Cardiovasc Electrophysiol* 2019;**30**:468-478.
8. Romero J, Cerrud-Rodriguez RC, Diaz JC, Rodriguez D, Arshad S, Alviz I, Cerna L, Rios S, Monhanty S, Natale A, Garcia MJ, Di Biase L. Oral anticoagulation after catheter ablation of atrial fibrillation and the associated risk of thromboembolic events and intracranial hemorrhage: a systematic review and meta-analysis. *J Cardiovasc Electrophysiol* 2019;**30**:1250-1257.
9. Andrade JG, Field T, Khairy P. Detection of occult atrial fibrillation in patients with embolic stroke of uncertain source: a work in progress. *Front Physiol* 2015;**6**:1-9.
10. Mesquita J, Cavaco D, Ferreira AM, Costa FM, Carmo P, Morgado F, Mendes M, Adragão P. Very long-term outcomes after a single catheter ablation procedure for the treatment of atrial fibrillation—the protective role of antiarrhythmic drug therapy. *J Interv Cardiac Electrophysiol* 2018;**52**:39-45.
11. Arbelo E, Brugada J, Blomström-Lundqvist C, Laroche C, Kautzner J, Pokushalov E, Raatikainen P, Efremidis M, Hindricks G, Barrera A, Maggioni A, Tavazzi L, Dagres N; on the behalf of the ESC-EHRA Atrial Fibrillation Ablation Long-term Registry Investigators. Contemporary management of patients undergoing atrial fibrillation ablation: in-hospital and 1-year follow-up findings from the ESC-EHRA atrial fibrillation ablation long-term registry. *Eur Heart J* 2017;**38**:1303-1316.
12. Leong-Sit P, Roux J-F, Zado E, Callans DJ, Garcia F, Lin D, Marchlinski FE, Bala R, Dixit S, Riley M, Hutchinson MD, Cooper J, Russo AM, Verdino R, Gerstenfeld EP. Antiarrhythmics after ablation of atrial fibrillation (5A Study). Six-month follow-up study. *Circ Arrhythm Electrophysiol* 2011;**4**:11-14.
13. Darkner S, Chen X, Hansen J, Pehrson S, Johannessen A, Nielsen JB, Svendsen JH. Recurrence of arrhythmia following short-term oral AMIOdarone after CATHeter ablation for atrial fibrillation: a double-blind, randomized, placebo-controlled study (AMIO-CAT trial). *Eur Heart J* 2014;**35**:3356-3364.
14. Gu J, Liu X, Tan H, Zhou L, Gu J, Jiang W, Wang Y, Liu Y. Extensive antiarrhythmic drugs after catheter ablation of persistent atrial fibrillation. *Acta Cardiol* 2012;**67**:407-414.
15. Hayashi M, Miyauchi Y, Iwasaki Y-K, Yodogawa K, Tsuboi I, Uetake S, Hayashi H, Takahashi K, Shimizu W. Three-month lower-dose flecainide after catheter ablation of atrial fibrillation. *Europace* 2014;**16**:1160-1167.
16. Kaitani K, Inoue K, Kobori A, Nakazawa Y, Ozawa T, Kurotobi T, Morishima I, Miura F, Watanabe T, Masuda M, Naito M, Fujimoto H, Nishida T, Furukawa Y, Shirayama T, Tanaka M, Okajima K, Yao T, Egami Y, Satomi K, Noda T, Miyamoto K, Haruna T, Kawaji T, Yoshizawa T, Toyota T, Yahata M, Nakai K, Sugiyama H, Higashi Y, Ito M, Horie M, Kusano KF, Shimizu W, Kamakura S, Morimoto T, Kimura T, Shizuta S. Efficacy of antiarrhythmic drugs short-term use after catheter ablation for atrial fibrillation (EAST-AF) trial. *Eur Heart J* 2016;**37**:610-618.
17. Xu X, Alida CT, Yu B. Administration of antiarrhythmic drugs to maintain sinus rhythm after catheter ablation for atrial fibrillation: a meta-analysis. *Cardiovasc Ther* 2015;**33**:242-246.
18. Xu B, Peng F, Tang W, Du Y, Guo H. Short-term antiarrhythmic drugs after catheter ablation for atrial fibrillation: a meta-analysis of randomized controlled trials. *Ann Pharmacother* 2016;**50**:697-705.
19. Chen W, Liu H, Ling Z, Xu Y, Fan J, Du H, Xiao P, Su L, Liu Z, Lan X, Zrenner B, Yin Y. Efficacy of short-term antiarrhythmic drugs use after catheter ablation of atrial fibrillation. A systematic review with meta-analyses and trial sequential analyses of randomized controlled trials. *PLoS One* 2016;**11**:e0156121.
20. Goldenberg GR, Burd D, Lodzinski P, Stabile G, Udell JA, Newman D, Shurrab M, Crystal E. Antiarrhythmic therapy as an adjuvant to promote post pulmonary vein isolation success—a meta-analysis. *J Interv Card Electrophysiol* 2016;**47**:171-176.
21. Kettering K, Gramley F. Catheter ablation of persistent atrial fibrillation. Beneficial effect of a short-term adjunctive amiodarone therapy on the long-term outcome. *Herzschr Elektrophys* 2018;**29**:133-140.
22. Duytschaever M, Demolder A, Philips T. Pulmonary vein isolation with vs. without continued antiarrhythmic drug treatment in subjects with Recurrent Atrial Fibrillation (POWDER AF): results from a multicenter randomized trial. *Eur Heart J* 2017;**0**:1-9.
23. Shantha G, Alyesh D, Ghanbari H, Yokokawa M, Saeed M, Cunnane R, Latchamsetty R, Crawford T, Jongnarangsin K, Bogun F, Pelosi F, Chugh A, Morady F, Oral H. Antiarrhythmic drug therapy and all-cause mortality after catheter ablation of atrial fibrillation: a propensity-matched analysis. *Heart Rhythm* 2019;**16**:1368-1373.