



# Possibilities of increasing the effectiveness of atrial fibrillation treatment (according to the results of studies presented at the European Society of Cardiology Congress, 2017)

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## Summary

*The review discusses six clinical trials on the diagnosis and treatment of atrial fibrillation, first presented at the scientific sessions of the Hot Line: Late-Breaking Clinical Trials of the Congress of the European Society of Cardiology in 2017. Positive results of these studies demonstrate the possibility of improving the quality of care for patients with atrial fibrillation during the stages of arrhythmia screening, cardioversion, maintaining sinus rhythm, and educational programs.*

## Keywords

*Atrial fibrillation, cardioversion, sinus rhythm maintenance, anticoagulant therapy, catheter ablation, screening.*

Atrial fibrillation (AF) is the most common stable cardiac arrhythmia that is currently diagnosed in millions of Europeans. Patients with AF report palpitations, reduced tolerance to physical exercise and life quality and have increased risk of stroke, chronic heart failure (CHF) and death [1]. Importance of AF problem increases together with the aging of popula-

tion and it starts to attract more attention of modern cardiology [2]. It is enough to mention that 6 (almost one third part) of studies selected for presentation at Hot Line: Late-Breaking Clinical Trials sessions of the European Society of Cardiology (ESC) Congress 2017 (Barcelona, Spain) were dedicated to diagnostics and treatment of AF. It is important to notice that

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the results of these studies turned out to be positive and could be successfully applicable for routine clinical practice thus increasing the quality of AF patients' management.

AF is caused by arterial hypertension, CHF, obesity requiring correction in the majority of patients [3-5], but the link between affecting these factors and arrhythmia's clinical course are not enough studied. Available pharmacological and interventional methods of AF treatment often fail to prevent its progression and complicate long-term maintenance of sinus rhythm. Structural remodeling of left atrium underlies the progression of AF from paroxysmal to constant form [6]. These ideas tested in the RACE 3 study helped to prove the hypothesis of improvement of AF treatment by modification of risk factors.

Open prospective study RACE 3 included patients with symptoms of recently persistent AF and/or CHF. Patients with left atrium diameter > 50 mm in parasternal axis were not included in this study. After randomization patients underwent conventional treatment (n=126) or aggressive correction of risk factors (n=119) that consisted of cardiologic rehabilitation (physical activity, restricted sodium consumption or calorie restriction in case of body mass index  $\geq 27$  kg/m<sup>2</sup>, or reduction of liquid consumption depending on CHF severity, regular follow-ups checking the adherence to treatment), administration of anti-mineralocorticoids, statins, angiotensin-converting enzyme antagonists and/or blockers of angiotensin type II receptors in maximal tolerated dose (target systolic blood pressure levels < 120 mm Hg). After at least 3 weeks of treatment electric cardioversion was performed, after it the therapy was continued for 12 months. The registration of sinus rhythm for at least 6/7 parts of time during 24-h electrocardiogram (ECG) monitoring within 7 days was considered as the primary endpoint and it was detected in 63% of patients in the group of conventional treatment and in 75% of patients who underwent aggressive correction of risk factors (p=0,021).

The hypothesis of RACE 3 study has been proved in general, meaning that precise correction of lifestyle and cardiovascular risk factors is effective, safe and possible to use, that it helps to maintain sinus rhythm in patients with recent persistent AF and not severe CHF. At the same time the advantages that have been achieved in the group of aggressive intervention have failed to be explained by positive influence of therapy on atrial remodeling, since after 1 year of treatment their dimensions remained unchanged. The authors

of this study proposed that heart remodeling appeared before AF manifestation, consequently even aggressive treatment resulted to be too late to influence heart dimensions. Two decades ago we saw significant reduction of left atrium in patients with paroxysmal AF after combination of effective hypotensive therapy (calcium channel blockers, angiotensin-converting enzyme inhibitors) and antiarrhythmic therapy (allapinin, ethacizine, propafenol, amiodarone and their combinations) [7]. It's possible that regression of left atrium remodeling in patients with AF is possible in case of use of antiarrhythmic agents providing stabilization of sinus rhythm.

The advantages that have been achieved by the group of aggressive intervention in the RACE 3 study were quite modest. Possibly, it was caused by refusal of any strong agent influencing AF like antiarrhythmic drugs or catheter ablation.

Optimal treatment of patients with combination of AF and CHF/left ventricular dysfunction remains a topic of discussion because up to date there are no clinical studies that could have demonstrated evident advantages of one therapeutic approach.

Patients with symptomatic paroxysmal or persistent AF with left ventricular ejection fraction (LVEF)  $\leq 35\%$ . All patients had implanted cardioverter defibrillator that allowed constant ECG monitoring. After randomization patients underwent radiofrequency catheter ablation of AF (isolation of pulmonary veins with additional linear ablation according to operator's indications) (n=153) or received conventional therapy (n=184) with consequent follow up for 3-60 months. The median of observation period was 37,8 months, and the frequency of the primary endpoint (death of any cause or admission to hospital due to CHF progression) was significantly lower in the group of ablation (28,5%) comparing with the control group (44,6%, relative risk (RR) 0,62, 95% confidence interval (CI) from 0,43 to 0,87 p=0,007). Mortality of any cause was registered in 13,4% of cases after catheter ablation versus 25% in the group of conventional therapy (RR 0,53, 95% CI 0,32-0,86, p=0,011). The frequency of admission to hospital due to CHF was 20,7% in the group of catheter ablation and 35,9% in the group of conventional therapy (RR 0,56, 95% CI 0,37-0,83; p=0,004). Mortality and frequency of admission to hospital due to cardiovascular causes in patients who underwent ablation was lower by 51% (0=0,008) and by 28% (p=0,05), respectively. Up to this study it has not been proved that ablation or antiarrhythmic agents could reduce mortality and frequency of admission to

hospital in patients with AF. The results of CASTLE AF study explain the feasibility of sinus rhythm maintenance in patients with AF and early stages of CHF. It is also possible that treatment costs may be reduced due to less frequent admission to hospital.

It is necessary to admit that antiarrhythmic drugs are used in the majority of AF cases for maintaining sinus rhythm. But is it possible to improve the prognosis of these patients in this case? 10 years ago we reported the results of our study that involved 223 patients aged up to 65 years with non-valvular persistent AF and CHF, II/III New York Heart Association (NYHA) functional class. These patients received the treatment maintaining sinus rhythm (n=113) or reducing the heart rate with persisting AF (n=110) during 2 years. The first therapeutic strategy resulted in significant reduction of general and cardiovascular mortality and reduced frequency of ischemic stroke. Sinus rhythm control was accompanied with increased tolerability of physical exercise, reduced clinical manifestations of CHF, increased LVEF and improved patients' life quality [8].

Cardioversion is as much important for AF treatment as anticoagulants are important for stroke prevention. Patients who have been prepared for AF cardioversion normally received heparin and/or warfarin for stroke risk reduction. Previous randomized prospective studies of Af cardioversion compared rivaroxaban (X-VerT) [9] and edoxaban (ENSURE-Af) [10] with heparin/warfarin and demonstrated comparable efficiency and safety of various anticoagulants together with low frequency of complications.

The EMANATE [11] study included 1500 patients with firstly diagnosed non-valvular Af that were supposed to undergo cardioversion. After randomization these patients received apixaban (5 mg twice per day or 2,5 mg twice per day if one of these two conditions was present: age  $\geq 80$  years, body weight  $\leq 60$  kg or plasma creatinine levels  $\geq 1,5$  mg/dL, n=753) or heparin and warfarin (n=747). Researchers could choose to set up the initial dose of apixaban as 10 mg (or 5 mg, respectively) if cardioversion was immediate. Within 30 days (90 days, if cardioversion was not performed) the number of strokes was 0 versus 6 (p=0,0164), the number of major bleeding was 3 versus 6, and of clinically significant ones was 11 versus 13 in the groups of apixaban and standard anticoagulation, respectively. There were no cases of systemic embolism in any of anticoagulant therapy regimens. Thrombi in left atrial appendage were visualized in 61 patients, and all of them received anticoagulants.

Follow-up examination was performed after  $37 \pm 11$  days and revealed resolution of thrombi in the groups of apixaban and heparin/warfarin in 52% and 56% of cases, respectively.

As many other similar studies, EMANATE had no enough statistic power to make final conclusions about the advantages of one anticoagulant therapy regimen over another for AF cardioversion. Taking into account predictably low number of complications of modern antithrombotic prevention, selection of the best anticoagulant would have required a randomized study with around 50000 participants that would be almost impossible to perform. Nevertheless, nowadays new oral anticoagulants are considered to be effective, safe, and convenient alternative to vitamin K antagonists for AF cardioversion.

AF is the cause of one out of five ischaemic strokes and these strokes result to be more dangerous comparing with the ones in patients without AF, they lead to severe disability and death in 60% and 20% of cases, respectively [12]. At least 2/3 of all strokes that occur in patients with AF can be prevented with administration of oral anticoagulants [13]. Only one half of patients with AF who are supposed to take anticoagulants receive them for real, and 80% of patients with ischemic stroke had inadequate anticoagulant therapy before its manifestation [14]. Underestimation of the role of oral anticoagulants in AF management is typical for countries with low economical development and it may be connected with insufficient education level of medical staff and patients [15].

The project IMPACT-AF involved 2281 patients with indications for anticoagulant therapy (the risk of stroke according to CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$ , rheumatic valvular lesions) from Argentina, Brazil, China, India and Romania [16]. After randomization the first group of patients (n=1184) participated in educational program (education, receiving information in printed form, webinars, phone calls, adherence control, clinical visits) apart from being prescribed with conventional treatment, whereas the control group (n=1092) underwent just standard treatment procedure. After approximately 12 months the percentage of patients of the first group who took oral anticoagulants increased from 68% to 80%, and in the control group it changed from 64% to 67%. During all observation period 11 and 21 strokes were registered in the group of intervention and in the control group, respectively. Multidirectional educational intervention aiming to improve the use of oral anticoagulants has led to significant increase of patients' compliance that

may improve stroke prevention in patients with AF. Approaches that had been used in this study were simple enough to be used in routine clinical practice at least in countries with moderate level of economical development.

Previous randomized studies reported that catheter isolation of pulmonary veins prevents AF more effectively than antiarrhythmic drugs [17]. But continuous cardiac rhythm monitoring was not used in these studies that did not allow precise estimation of AF duration. Neither one of the studies that evaluated ablation for AF treatment did not use life quality as the primary endpoint, although relieving of symptoms is the main result of AF ablation. Instead of it AF recurrence that lasted 30 seconds was taken as the primary endpoint, and it hardly corresponded to successful therapy. The main objective of the CAPTAF study was comparison of AF treatment using catheter ablation or antiarrhythmic drugs, and life quality of patients was taken as primary endpoint.

The CAPTAF included 155 patients with AF who failed to maintain sinus rhythm with antiarrhythmic drugs treatment and had at least one symptomatic episode of paroxysmal AF that required cardioversion during previous 12 months. All patients had implantable cardiac rhythm monitor. After randomization 79 patients underwent catheter isolation of pulmonary veins or received antiarrhythmic drug therapy according to the current guidelines ( $n=76$ ). Positive change of general health condition according to the Short Form 36 estimated during the following 12 months (primary endpoint) was significantly higher in the group of ablation: 11,0 points versus 3,1 in the group of pharmacological treatment ( $p=0,0084$ ). Severity of AF symptoms estimated using the classification of the European Heart Rhythm Association 12 months after was reduced to higher extent in the group of ablation (from  $3,0\pm 0,7$  to  $1,6\pm 0,8$ ) comparing with the group where patients received antiarrhythmic drugs (from  $2,9\pm 0,7$  to  $2,1\pm 1,1$ ;  $p=0,0079$ ). At the same time there was no statistically significant difference of reduction of AF burden in studied groups. Lack of statistically significant differences of AF burden reduction between the groups indicates that other mechanisms could explain better the improvement of life quality and symptoms that was reached by pulmonary veins' isolation. The authors of this work hypothesized that improved life quality in the group of ablation could be related to the absence of antiarrhythmic drugs' adverse effects. The researchers supposed that the life quality and not the number of AF episodes longer

than 30 s should be the primary endpoint of future studies of therapy for sinus rhythm maintenance.

Asymptomatic AF is associated with higher risk of thromboembolism comparing with AF manifesting with common symptoms due to lower awareness of doctors and patients [18]. AF that appears from time to time (paroxysmal AF) can disappear spontaneously but it is accompanied with increased risk of stroke and requires prescription of antithrombotic therapy identical to the one used for permanent AF [19]. Current ESC guidelines on Af management suggest performing primary screening of this arrhythmia in population of people older than 65 years checking their pulse and registering ECG [1]. Several clinical studies aim to estimate the possibilities of various portable monitors to detect asymptomatic/manifesting with few symptoms AF.

REHEARSE-AF [20] project consisted of AF screening in people without AF, having  $CHA_2DS_2$ -VASc score  $\geq 2$ , and aged  $\geq 65$  years that used cardiomonitor AliveCor Kardia ( $n=501$ ) or conventional management ( $n=500$ ). Cardiomonitor registered ECG after person touched it with two fingers of right and left hands and transferred it to iPod supporting WiFi technology. This diagnostic procedure was performed twice per week during 12 months and ECG registration with automatic description, consultation of physiologist or/and cardiologist was supplied in case of symptoms' manifestation. Af detection was considered as the primary endpoint and it was registered in 19 patients in the group that used cardiomonitor and in 5 patients from the group of conventional treatment (RR 3,9 95% CI 1,4-10,4;  $p=0,007$ ). The number of registered strokes/transitory ischemic attacks/systemic embolism cases was 6 versus 10 in cardiomonitor and control groups, respectively (RR 0,61 95% CI 0,22-1,69,  $p=0,34$ ). This gadget for easy distant ECG interpretation allows detection of AF in elderly people with increased stroke risk in outpatient conditions more frequently.

Patients demonstrated high compliance to ECG control since more than 2/3 of them made it twice per week at least during 75% of time of the study. Elderly people reported their confidence in cardiomonitor registrations and satisfaction with its presence. According to the researchers, if the use of tested observation program was reasonable from clinical and economical point of view, it would be used in target population.

These studies demonstrate significant progress of arrhythmology in diagnostics and treatment of AF.

After 15 years of refusal of aggressive interventions for sinus rhythm maintenance for reducing heart rate in persisting AF the first strategy starts to demonstrate some optimistic trends. The approaches of AF detection, cardioversion, prevention of AF relapses, educational programs are further developing. Improvement of AF eradication using catheter ablation and, possibly, creating more safe and effective antiarrhythmic agents would allow improving life quality and prognosis of the population of people with AF that is growing fast.

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## References

1. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37(38):2893-962.
2. Morillo CA, Banerjee A, Perel P, et al. Atrial fibrillation: the current epidemic. *J Geriatr Cardiol*. 2017;14(3):195-203.
3. Dzeshka MS, Shantsila A, Shantsila E, Lip GYH. Atrial Fibrillation and Hypertension. *Hypertension*. 2017;70(5):854-61.
4. Batul SA, Gopinathannair R. Atrial Fibrillation in Heart Failure: a Therapeutic Challenge of Our Times. *Korean Circ J*. 2017;47(5):644-62.
5. Lavie CJ, Pandey A, Lau DH, et al. Obesity and Atrial Fibrillation Prevalence, Pathogenesis, and Prognosis: Effects of Weight Loss and Exercise. *J Am Coll Cardiol*. 2017;70(16):2022-35.
6. Lau DH, Nattel S, Kalman JM, Sanders P. Modifiable Risk Factors and Atrial Fibrillation. *Circulation*. 2017;136(6):583-96.
7. Kanorsky SG, Skibitsky VV, Fedorov AV. Correction of Structural Changes of the Left Heart in Patients With Effective Preventive Treatment of Recurrent Attacks of Paroxysmal Atrial Fibrillation. *Kardiologija*. 1998;38(2):37-42. Russian
8. Kanorsky SG, Kruchinova OA, Zingilevsky KB. Advantages of Restoration and Maintenance of Sinus Rhythm in Middle Aged Patients With Atrial Fibrillation and Chronic Heart Failure. *Kardiologija*. 2006;46(9):31-35. Russian
9. Cappato R, Ezekowitz MD, Klein AL, et al. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. *Eur Heart J*. 2014;35(47):3346-55.
10. Goette A, Merino JL, Ezekowitz MD, et al. Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. See comment in PubMed Commons below *Lancet*. 2016;388(10055):1995-2003.
11. Ezekowitz MD, Pollack CV, Sanders P, et al. Apixaban compared with parenteral heparin and/or vitamin K antagonist in patients with nonvalvular atrial fibrillation undergoing cardioversion: Rationale and design of the EMANATE trial. See comment in PubMed Commons below *Am Heart J*. 2016;179:59-68.
12. Gladstone DJ, Bui E, Fang J, et al. Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. *Stroke*. 2009;40(1):235-40.
13. 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(12):857-67.
14. Xian Y, O'Brien EC, Liang L, et al. Association of Preceding Antithrombotic Treatment With Acute Ischemic Stroke Severity and In-Hospital Outcomes Among Patients With Atrial Fibrillation. *JAMA*. 2017;317(10):1057-67.
15. Glauser TA, Barnes J, Nevins H, Cerenzia W. The Educational Needs of Clinicians Regarding Anticoagulation Therapy for Prevention of Thromboembolism and Stroke in Patients With Atrial Fibrillation. *Am J Med Qual*. 2016;31(1):38-46.
16. Vinereanu D, Lopes RD, Bahit MC, et al. A multifaceted intervention to improve treatment with oral anticoagulants in atrial fibrillation (IMPACT-AF): an international, cluster-randomised trial. *Lancet* 2017;390:1737-46.
17. Kirchhof P, Calkins H. Catheter ablation in patients with persistent atrial fibrillation. *Eur Heart J*. 2017;38(1):20-26.
18. Siontis KC, Gersh BJ, Killian JM, et al. Typical, atypical, and asymptomatic presentations of new-onset atrial fibrillation in the community: Characteristics and prognostic implications. *Heart Rhythm*. 2016;13(7):1418-24.
19. Friberg L, Hammar N, Rosenqvist M. Stroke in paroxysmal atrial fibrillation: report from the Stockholm Cohort of Atrial Fibrillation. *Eur Heart J*. 2010;31(8):967-75.
20. Halcox JPJ, Wareham K, Cardew A, et al. Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation: The REHEARSE-AF Study. *Circulation*. 2017 Aug 28. [Epub ahead of print]