

Timing of cardioversion in atrial fibrillation: the sooner the better?

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Management of recent-onset (<36 h) atrial fibrillation (AF) in the emergency room is highly variable, particularly concerning the type and timing of cardioversion, and the logistics of the treatment pathway. In clinical practice, it is fairly common for patients with recent-onset AF an attempt at re-establishing sinus rhythm, either with electric or pharmacologic cardioversion, as soon as feasible. Nonetheless, a ‘wait-and-see’ approach, and potentially delayed cardioversion, could represent a valid alternative to early cardioversion, considering that, often, in recent-onset AF, sinus rhythm is re-established spontaneously, thus repealing the need for active cardioversion, hence avoiding the possible risks of treatment. These concepts form the rationale for a recent multicentric randomized trial, Rate Control vs. Electrical Cardioversion Trial 7 - Acute Cardioversion vs. Wait and See (RACE 7 ACWAS), comparing the efficacy of delayed cardioversion, within 48 h from symptoms onset, in case of lack of spontaneous conversion, with early cardioversion in symptomatic patients with recent-onset AF. In patients presenting to the emergency department with recent-onset, symptomatic AF, a wait-and-see approach was non-inferior to early cardioversion in maintaining the sinus rhythm at 4 weeks. Nonetheless a system employing a delayed cardioversion strategy increases the costs of treatment, complicates the treatment pathway, and could represent a psychological burden for the patients. Accordingly, delayed cardioversion could not represent a practical choice for many hospitals with limited resources and without an adequate outpatient organization.

Introduction

Recent-onset atrial fibrillation (AF) (within 36 h from the onset of related symptoms) is a frequent cause of presentation in the emergency room, with a not negligible impact on the care and economic burden of the health system.¹ Regarding this scenario, in the most recent European guidelines on AF issued in 2016, there are no specific recommendations on the use and timing of cardioversion.² In the context of this shortcoming, the management of recently developed AF in the emergency room is highly heterogeneous, especially with regard to cardioversion (type and

timing) and the logistics of the treatment pathway. In clinical practice, a relatively common approach in the management of patients with recent-onset AF is to achieve sinus rhythm by electrical or pharmacological cardioversion as early as possible. However, a ‘wait-and-see’ approach with possible delayed cardioversion, could represent a valid alternative to early cardioversion, in consideration of the fact that often in the recent-onset AF the sinus rhythm is spontaneously restored, making active cardioversion unnecessary and therefore avoiding over-treatment and its potential risks. Based on this rationale, a recent multicentre, randomized Rate Control vs. Electrical Cardioversion Trial 7 - Acute Cardioversion vs. Wait and See (RACE 7 ACWAS) trial assessed whether the effectiveness of delayed cardioversion performed within 48 h of symptoms in case of failure spontaneous restoration of sinus rhythm

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was not inferior than that of early cardioversion in symptomatic patients with recent-onset AF.³

Early or delayed cardioversion of atrial fibrillation: pros and cons

For patients with recent-onset AF, there are several advantages to applying the 'wait-and-see' strategy, consisting of waiting for spontaneous conversion to sinus rhythm and only if the latter does not occur delayed electrical or pharmacological cardioversion will be performed within 48 h from the onset of symptoms. In particular, this strategy allows to avoid an excess of cardioversion procedures and to reduce the time spent in the emergency room during a single access. Furthermore, observing the spontaneous conversion to sinus rhythm allows to avoid classifying AF as persistent, conditioning any future choices on rhythm control strategies.² In addition, the patient's experience that his/her arrhythmia ends spontaneously could optimize its management and treatment, with the potential to avoid unnecessary future recourse to the emergency room in case of recurrence of arrhythmic episodes. On the other hand, the waiting strategy with delayed cardioversion could have several disadvantages. The most relevant is to increase the number of emergency room visits and outpatient visits, leading to an increased total use of resources and more demanding logistics, as well as a potential greater discomfort for the patient. The greater difficulty of the patient to return to the hospital for the check within 48 h, could lead to delays that would complicate the management of AF, since in patients who were not on chronic anticoagulant therapy before the arrhythmic episode, the transoesophageal echocardiogram or alternatively the prolongation of anticoagulant therapy for at least 3 weeks are required before the cardioversion can be performed at more than 48 h from symptoms onset.² Finally, the delay in proceeding to cardioversion involves a longer time in AF that could be associated with greater risks of thromboembolic events, especially in patients who were not on chronic anticoagulant therapy,⁴ or haemodynamic complications, especially in patients with underlying structural heart disease.

On the contrary, the early cardioversion strategy, by shortening the period preceding the conversion to the sinus rhythm, has the potential advantage of eliminating symptoms earlier and preventing complications such as heart failure, syncope, cerebrovascular ischaemic events, and especially the progression towards persistent AF. Furthermore, an early pharmacological cardioversion strategy could test the safety and efficacy of antiarrhythmic drugs, which can then be prescribed for self-administration by the patient ('pill-in-the-pocket' approach), reducing the probability of future access to the emergency room.^{5,6} Finally, the strategy of immediate cardioversion could improve the patient's degree of satisfaction for the treatment received for his/her arrhythmia, as well as for the simplification of his diagnostic-therapeutic pathway.

Effectiveness of delayed compared with early cardioversion

The effectiveness of the treatment of new-onset AF with immediate cardioversion was compared with that of a wait-and-see approach and possible delayed cardioversion (within 48 h) in the RACE 7 ACWAS study.³ The latter is a randomized non-inferiority trial that included 437 patients with recent-onset (<36 h) AF, both first episode and recurrent event, symptomatic, haemodynamically stable with no signs of myocardial ischaemia or no history of persistent AF (prior episodes lasting >48 h), who presented to the emergency room of 15 hospitals in the Netherlands from October 2014 to September 2018. Patients included were randomized with a 1:1 ratio to a 'wait-and-see' approach with delayed cardioversion, but still carried out within 48 h, or to standard treatment with early (immediate) cardioversion.

Patients randomized to the delayed cardioversion arm were treated with a pharmacological approach for the rate control with oral or intravenous beta-blocker drugs, calcium channel blockers, or digitalis. These drugs were administered in increasing doses until the symptoms regressed and a heart rate less than or equal to 110 b.p.m. was reached. Subsequently, patients deemed clinically stable were discharged and an outpatient visit was scheduled at as close as possible to 48 h after the onset of AF-related symptoms. During this planned visit an electrocardiogram was performed to check the heart rhythm and if the AF was still present, the patient was sent back to the emergency room to undergo delayed cardioversion.

Patients randomized to the early cardioversion arm underwent pharmacological cardioversion, preferably with flecainide. Electrical cardioversion was performed only in patients with contraindications to the pharmacological one or in those in whom the pharmacological cardioversion failed or had previously been ineffective.

Patients enrolled in the RACE 7 ACWAS trial were mostly young with an average age of 65 ± 11 years, 40% were female and 44% were at their first episode of AF. Of note, about one-third of patients (36%) had a low stroke risk as indicated by their CHA₂DS₂-VASc score less than 2. At enrolment, the anticoagulant therapy was already assumed chronically in 40% of patients and was started in 29%. To understand the proportion of patients to whom the methodology and the results of the study could be applied, a log screening was completed in two of the included centres, which showed an exclusion from the study of two-thirds of the patients admitted with AF to the emergency room. The main reason for this exclusion was the duration of AF greater than 36 h followed by the presence in the history of previous episodes of persistent AF. In the delayed cardioversion group, spontaneous conversion to sinus rhythm occurred in 69% of patients. This result was associated with a non-inferior 4-week efficacy of the delayed vs. early cardioversion. In fact, the primary endpoint of the trial consisting of the proportion of patients with sinus rhythm at the electrocardiogram performed during the 4-week visit was found in 91% of patients in the delayed cardioversion group vs. 94% of the group randomized to the early

cardioversion arm (the difference between groups -2.9 percentage points; 95% confidence interval -8.2 to 2.2 ; $P=0.005$ for non-inferiority). Emergency room visits for AF recurrence were observed in 7% of patients in both groups. No significant differences were observed between the two cardioversion groups in the incidence of cardiovascular complications. The total care time for enrolled patients was 120 min (range 60-253) in the delayed cardioversion group and 158 min (range 110-228) in the early cardioversion group. The telemetry recording of the electrocardiogram performed during the 4 weeks after randomization for 335 patients documented a similar recurrence of AF in 30% and 29% of patients in the delayed and early cardioversion groups, respectively. Finally, the scores used in the study to evaluate the quality of life did not reveal differences between the two groups. However, the patient's quality of life assessment was not performed early at the time the patient was discharged and rescheduled for the next rhythm assessment visit in the case of patients randomized to the delayed cardioversion group.

Early or delayed cardioversion of atrial fibrillation: summary and practical suggestions

In summary, the RACE 7 ACWAS trial showed that spontaneous conversion to sinus rhythm occurs frequently in patients with recent-onset AF treated with a wait-and-see approach and delayed cardioversion, markedly reducing the need to perform an electrical or pharmacological immediate cardioversion. This advantage has been associated with a non-inferior efficacy than that of early cardioversion, as measured by the proportion of patients who remained in sinus rhythm at one month after randomization. However, this efficacy result was obtained with a markedly reduced efficiency of the delayed cardioversion strategy, since it was necessary to implement a greater number of resources. In fact, compared to patients treated with early cardioversion, those who underwent delayed cardioversion needed additional outpatient visits to check the rhythm and new access to the emergency room for those who had persisted in AF to undergo cardioversion. Based on the numbers that emerged in the RACE 7 ACWAS trial, 130 emergency room access would be required to attempt to achieve the goal of sinus rhythm at admission, applying the delayed cardioversion strategy on 100 patients with recent-onset AF (100 for the first access plus 30 for the second access for those not spontaneously cardioverted) in addition to 100 outpatient visits performed to check the rhythm, compared to 100 accesses to the emergency room that would be sufficient for patients treated with early cardioversion. The reduced efficiency of a system that adopts the delayed cardioversion strategy has the potential effects of increasing costs, of making the logistics of assistance more complex, and of aggravating

the material and psychological commitment for patients. Therefore, the delayed cardioversion approach may not be practical in many hospitals with limited resources and with an unsuitable outpatient organization. Another factor that could limit the applicability of delayed cardioversion in clinical practice is the lack of reliable data on the safety of this approach. In fact, the RACE 7 ACWAS trial does not have a design with adequate statistical power to demonstrate a possible difference in cardiovascular events, which were similar between the two compared groups.

In view of both these limitations and the benefits associated with delayed cardioversion, in current clinical practice this approach could be considered in patients with recent-onset AF (<36 h) with a higher probability of spontaneous cardioversion and with a low risk of cardiovascular events. Unfortunately, precise predictive models have not been established, but on the basis of available studies and factors that can reduce the safety in deferring cardioversion,⁷ patients in whom reasonably consider the use of the wait-and-see approach and delayed cardioversion could include those with AF onset less than 24 h, without heart failure or significant structural disease and with a moderate or low risk of stroke.

Conflict of interest: none declared.

References

- Meyre P, Blum S, Berger S, Aeschbacher S, Schoepfer H, Briel M, Osswald S, Conen D. Risk of hospital admissions in patients with atrial fibrillation: a systematic review and meta-analysis. *Can J Cardiol* 2019;**35**:1332-1343.
- Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener H-C, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorennek B, Guenoun M, Hohnloser SH, Kolh P, Lip GYH, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016;**18**:1609-1678.
- Pluymaekers NAHA, Dudink EAMP, Luermans JGLM, Meeder JG, Lenderink T, Widdershoven J, Bucx JJJ, Rienstra M, Kamp O, Van Opstal JM, Alings M, Oomen A, Kirchhof CJ, Van Dijk VF, Ramanna H, Liem A, Dekker LR, Essers BAB, Tijssen JGP, Van Gelder IC, Crijns HJGM. Early or delayed cardioversion in recent-onset atrial fibrillation. *N Engl J Med* 2019;**380**:1499-1508.
- Nuotio I, Hartikainen JE, Grönberg T, Biancari F, Airaksinen KE. Time to cardioversion for acute atrial fibrillation and thromboembolic complications. *JAMA* 2014;**312**:647-649.
- Alboni P, Botto GL, Baldi N, Luzi M, Russo V, Gianfranchi L, Marchi P, Calzolari M, Solano A, Baroffio R, Gaggioli G. Outpatient treatment of recent-onset atrial fibrillation with the "pill-in-the-pocket" approach. *N Engl J Med* 2004;**351**:2384-2391.
- Capucci A, Villani GQ, Piepoli MF. Reproducible efficacy of loading oral propafenone in restoring sinus rhythm in patients with paroxysmal atrial fibrillation. *Am J Cardiol* 2003;**92**:1345-1347.
- Danias PG, Caulfield TA, Weigner MJ, Silverman DI, Manning WJ. Likelihood of spontaneous conversion of atrial fibrillation to sinus rhythm. *J Am Coll Cardiol* 1998;**31**:588-592.