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DEBATE

Is delayed cardioversion the better approach in recent-onset atrial fibrillation? No

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Abstract

Symptomatic atrial fibrillation (AF) is a common cause of emergency department (ED) referrals. In case of hemodynamic stability, the choice to either perform early cardioversion (pharmacologic or electrical) or to prescribe rate-lowering drugs and differ any attempts to restore sinus rhythm (i.e., wait-and-see approach) has been widely debated. Results of the recent Rate Control versus Electrical Cardioversion Trial 7-Acute Cardioversion versus Wait and See (RACE 7 ACWAS) have been considered a strong argument in favor of the wait-and-see approach. In this debate, we discuss several issues that would support early cardioversion, ranging from patients' satisfaction and costs to concerns about safety. Furthermore, the wait-and-see approach may translate into a missed opportunity to encourage widespread use of a "pill-in-the-pocket" home treatment: this underused option could allow rapid solving of many AF episodes, potentially avoiding future ED referrals. Our opinion is that a delayed cardioversion may introduce unneeded complications in the straightforward management of a common clinical problem. Therefore, early cardioversion should continue to be the preferred option because of its proven efficacy, safety and convenience.

Keywords Atrial fibrillation · Cardioversion · Rate control · Rhythm control · Wait-and-see · Pill-in-the-pocket

The atrial fibrillation (AF) epidemic is a growing concern, with an estimated lifetime risk of 37% [1]. Emergency department (ED) visits are a common occurrence in AF patients' lives and a major driver of AF-related costs. Of all ED visits in the USA, 0.5% are due to this arrhythmia, mainly because of symptomatic episodes [2].

Several clinical issues should be addressed in the care of AF patients in the ED [3]. First of all, acute rate and rhythm control should be pursued to achieve hemodynamic stability. Precipitant triggers (thyrotoxicosis, electrolyte imbalances) should be actively identified and corrected. Stroke risk should be estimated by means of established tools, such as the CHA_2DS_2-VASc, and anticoagulation provided accordingly [4–8].

In case of hemodynamic stability, the choice between rate and rhythm control strategies confronts physicians with potential clinical equipoise, because many AF episodes terminate spontaneously.

In the recent Rate Control versus Electrical Cardioversion Trial 7-Acute Cardioversion versus Wait and See (RACE 7 ACWAS), 437 hemodynamically stable symptomatic patients with recent-onset (< 36 h) AF were randomized to either early cardioversion or a wait-and-see approach [9]. The former strategy consisted of pharmacologic cardioversion, primarily with a flecainide infusion, or electrical cardioversion, in case antiarrhythmic drugs were contraindicated or ineffective. The latter approach involved administering rate-control drugs and scheduling an outpatient clinic visit the day after presentation; in case AF persisted, patients were referred again to the ED for cardioversion.

The wait-and-see approach showed noninferior efficacy for the primary endpoint of sinus rhythm after 4 weeks. The major reported advantage was that this delayed strategy enabled spontaneous restoration of sinus rhythm within 48 h in 69% of cases, avoiding complications related to antiarrhythmic drug use, sedation, or electrical shock delivery. In contrast, only 16% of patients in the early cardioversion group spontaneously converted to sinus rhythm before cardioversion. Furthermore, the authors reported similar quality

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of life after 4 weeks, as measured by the Atrial Fibrillation Effect on Quality-of-Life questionnaire (AFEQT), irrespective of treatment group assignment [10].

So, shall we routinely apply the wait-and-see approach in the management of symptomatic, hemodynamically stable AF patients presenting to the ED? We do not believe so [11].

Our first concern regards patients' satisfaction and quality of life In fact, patients are coming to the ED with an active health issue which is causing symptoms. It is likely that sending patients back home, without solving the problem that motivated them to come to the hospital, could be perceived as an underestimation of their clinical problem and of their value. In RACE 7 ACWAS, quality of life was only measured after 4 weeks. Such a late evaluation may have not captured acute patients' satisfaction and the perceived effectiveness of ED treatment [12]. In the era of patient-centered outcomes, these elements may prove fundamental in the process of building a successful patient–physician alliance.

Given the dynamic nature of patient experience in AF, a meaningful quality of life assessment should have included an immediate evaluation at the moment of ED discharge, as well as earlier than after 1 month. The finding in RACE 7 ACWAS that quality of life did not differ after 4 weeks between the early and the delayed groups may simply reflect AF's tendency to recur. In fact, the proportion of patients experiencing an AF's relapse was similar regardless of the treatment strategy.

The second concern regards the practical feasibility of the wait-and-see approach, as designed in the present trial Scheduling visits to the outpatient cardiology clinic for every patient coming to the ED with symptomatic AF may prove impractical in many hospitals with inadequate human resources. An expansion of already overloaded waiting lists can easily be expected. Furthermore, costs could be exponentially raised, weighing that the delayed approach would add to every ED access for AF one outpatient clinic visit plus a second ED referral in case of AF persistence (as in 28% of patients in RACE 7 ACWAS). We strongly believe that an economic analysis, which is lacking in the trial, would enhance clinical decision-making.

Our third concern is that patients' safety may be compromised The risk of several dreadful AF complications, such as stroke or heart failure, increases over time. To illustrate, in a large Finnish study of patients undergoing successful cardioversion in the ED within the first 48 h of AF symptoms' onset, risk of thromboembolic complications was almost quadrupled when time to cardioversion was 12 h or longer (1.1% vs. 0.3%) [13]. Accumulating evidence suggests that even spontaneous conversions to sinus rhythm are associated with an increased risk of stroke. This risk seems to correlate with AF burden and becomes particularly relevant after 24 h [14, 15]. Consistently, observational studies reported that the presence of sinus rhythm at the moment of ED discharge predicts a lower risk of AF-related adverse events [16]. Although in RACE 7 ACWAS the rate of cardiovascular complications was low and similar in the two treatment strategies, the trial was not statistically powered to assess safety.

The fourth concern is related to the potential for AF progression Animal models and human studies showed that longer AF episodes are associated with a greater propensity to AF inducibility and stability, as resumed in the motto "AF begets AF" [17]. These observations can be explained by AF-induced electrical remodeling, which is characterized by shortening of the atrial effective refractory period. Although remodeling appears to be reversible for the first few days, it may become fixed as soon as atrial fibrosis and dilation develop, driving progression from paroxysmal to persistent or permanent AF forms. An early aggressive rhythm control approach may halt these maladaptive processes and translate into improved clinical outcomes [18, 19]. RACE 7 ACWAS did not reveal a greater propensity for AF recurrence and progression in the wait-and-see group. However, continuous heart rhythm monitoring was unavailable and the trial did not have adequate statistical power to detect this relevant clinical endpoint.

Finally, the wait-and-see strategy may translate into a missed opportunity In fact, the ED is the ideal setting in which safety and effectiveness of oral antiarrhythmic drugs (mainly class Ic drugs, flecainide or propafenone) can be tested, enabling future prescription of these drugs for on-demand self-administration at home, also known as the "pill in the pocket" approach [20–22]. This underused option proved to be very effective in terminating AF episodes rapidly (i.e., within 2–3 h), allowing home-solving of most AF paroxysms and thus markedly reducing ED referrals [23]. The main concern associated with prescription of class Ic drugs for this practice is the potential for AF conversion to atrial flutter with 1:1 atrio-ventricular conduction ratio. Risk of this complication is generally low (i.e., $< 1\%$) and it can be significantly reduced by recommending physical rest for some hours after anti-arrhythmic drug consumption, to reduce sympathetic nervous system activity along with its potentially dangerous facilitating effects on the atrio-ventricular conduction system. Pitifully, in RACE 7 ACWAS, the "pill-in-the-pocket" approach was omitted.

Therefore, for all the reasons mentioned above, we firmly believe that a wait-and-see approach does not offer significant advantages over an early cardioversion strategy [11]. Conversion to sinus rhythm can be successfully and rapidly achieved during the first ED visit in most patients with symptomatic, recent-onset AF. Therefore, a delayed cardioversion strategy would introduce an unneeded and potentially disadvantageous complexity in the management of a straightforward clinical problem. In addition, use of a class Ic drug's oral loading dose for a "pill-in-the-pocket"

treatment should be encouraged in appropriate patients, because of its demonstrated efficacy, convenience and acceptable safety.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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