

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

APRIL 18, 2019

VOL. 380 NO. 16

Early or Delayed Cardioversion in Recent-Onset Atrial Fibrillation

N.A.H.A. Pluymaekers, E.A.M.P. Dudink, J.G.L.M. Luermans, J.G. Meeder, T. Lenderink, J. Widdershoven, J.J.J. Bucx, M. Rienstra, O. Kamp, J.M. Van Opstal, M. Alings, A. Oomen, C.J. Kirchhof, V.F. Van Dijk, H. Ramanna, A. Liem, L.R. Dekker, B.A.B. Essers, J.G.P. Tijssen, I.C. Van Gelder, and H.J.G.M. Crijns, for the RACE 7 ACWAS Investigators*

ABSTRACT

BACKGROUND

Patients with recent-onset atrial fibrillation commonly undergo immediate restoration of sinus rhythm by pharmacologic or electrical cardioversion. However, whether immediate restoration of sinus rhythm is necessary is not known, since atrial fibrillation often terminates spontaneously.

METHODS

In a multicenter, randomized, open-label, noninferiority trial, we randomly assigned patients with hemodynamically stable, recent-onset (<36 hours), symptomatic atrial fibrillation in the emergency department to be treated with a wait-and-see approach (delayed-cardioversion group) or early cardioversion. The wait-and-see approach involved initial treatment with rate-control medication only and delayed cardioversion if the atrial fibrillation did not resolve within 48 hours. The primary end point was the presence of sinus rhythm at 4 weeks. Noninferiority would be shown if the lower limit of the 95% confidence interval for the between-group difference in the primary end point in percentage points was more than -10.

RESULTS

The presence of sinus rhythm at 4 weeks occurred in 193 of 212 patients (91%) in the delayed-cardioversion group and in 202 of 215 (94%) in the early-cardioversion group (between-group difference, -2.9 percentage points; 95% confidence interval [CI], -8.2 to 2.2; $P=0.005$ for noninferiority). In the delayed-cardioversion group, conversion to sinus rhythm within 48 hours occurred spontaneously in 150 of 218 patients (69%) and after delayed cardioversion in 61 patients (28%). In the early-cardioversion group, conversion to sinus rhythm occurred spontaneously before the initiation of cardioversion in 36 of 219 patients (16%) and after cardioversion in 171 patients (78%). Among the patients who completed remote monitoring during 4 weeks of follow-up, a recurrence of atrial fibrillation occurred in 49 of 164 patients (30%) in the delayed-cardioversion group and in 50 of 171 (29%) in the early-cardioversion group. Within 4 weeks after randomization, cardiovascular complications occurred in 10 patients and 8 patients, respectively.

CONCLUSIONS

In patients presenting to the emergency department with recent-onset, symptomatic atrial fibrillation, a wait-and-see approach was noninferior to early cardioversion in achieving a return to sinus rhythm at 4 weeks. (Funded by the Netherlands Organization for Health Research and Development and others; RACE 7 ACWAS ClinicalTrials.gov number, NCT02248753.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Crijns at the Department of Cardiology, Maastricht University Medical Center, P. Debye-laan 25, 6229 HX Maastricht, the Netherlands, or at hjgm.crijns@mumc.nl.

*A complete list of investigators in the RACE 7 ACWAS trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Pluymaekers and Dudink contributed equally to this article.

This article was published on March 18, 2019, at NEJM.org.

N Engl J Med 2019;380:1499-508.

DOI: 10.1056/NEJMoa1900353

Copyright © 2019 Massachusetts Medical Society.

 A Quick Take is available at [NEJM.org](https://www.nejm.org)

PATIENTS WITH RECENT-ONSET, SYMPTOMATIC atrial fibrillation commonly undergo immediate restoration of sinus rhythm by means of pharmacologic or electrical cardioversion.¹⁻³ However, it is questionable whether immediate restoration of sinus rhythm is necessary, since atrial fibrillation often terminates spontaneously.⁴⁻⁹ Alternatively, a wait-and-see approach that includes the administration of rate-control medication and delayed cardioversion only if necessary may avoid hospitalization and overtreatment. Therefore, we conducted a multicenter, randomized trial, RACE 7 ACWAS (Rate Control versus Electrical Cardioversion Trial 7—Acute Cardioversion versus Wait and See), to find out whether a wait-and-see approach would be noninferior to early cardioversion for obtaining sinus rhythm.

METHODS

TRIAL OVERSIGHT

We conducted this noninferiority trial in the cardiology departments of 15 hospitals in the Netherlands, including 3 academic hospitals, 8 non-academic teaching hospitals, and 4 nonteaching hospitals. The trial was initiated by the investigators and coordinated by the Maastricht University Medical Center. The trial was approved by the institutional review board at the medical center; the review board at each of the participating sites approved the protocol (available with the full text of this article at [NEJM.org](https://www.nejm.org)). A detailed overview of the trial design has been reported previously.¹⁰ All the patients provided written informed consent.

Staff members of the independent Clinical Trial Center Maastricht performed the trial monitoring and data management. The trial was supported by the Netherlands Organization for Health Research and Development—Health Care Efficiency Research Program and Maastricht University Medical Center. Boehringer Ingelheim provided some devices for remote monitoring of patients by electrocardiography (ECG) but had no role in the design or execution of the trial; company representatives did not review the protocol or the manuscript. Investigators from the Department of Cardiology affiliated with the Heart and Vascular Center at the Maastricht University Medical Center designed the trial, collected and managed the data, and performed the statistical analyses. The writing committee wrote the manuscript, and all the steering committee members made the decision

to submit it for publication. The authors had unrestricted access to the data and vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol.

PATIENTS

From October 2014 through September 2018, we enrolled adults (≥ 18 years of age) who had presented to the emergency department with hemodynamically stable, symptomatic, recent-onset (< 36 hours), first-detected or recurrent atrial fibrillation, without signs of myocardial ischemia or a history of persistent atrial fibrillation (for the purpose of this trial defined as lasting for > 48 hours). All the patients qualified as being candidates for either a wait-and-see approach or early cardioversion. Previous cardioversion did not exclude a patient from the trial. Details regarding the inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix, available at [NEJM.org](https://www.nejm.org).

RANDOMIZATION AND TREATMENT

Patients were randomly assigned in a 1:1 ratio to the wait-and-see approach (delayed-cardioversion group) or to standard care of early cardioversion (early-cardioversion group). Randomization was performed with the use of a centralized Web-based system. Patients and attending physicians were aware of the trial-group assignments.

The wait-and-see approach consisted of the administration of rate-control medication, including intravenous or oral β -adrenergic-receptor blocking agents, nondihydropyridine calcium-channel blockers, or digoxin. These medications were given in increasing doses to obtain relief of symptoms and a heart rate of 110 beats per minute or less.¹¹ Patients were discharged when their condition was determined to be clinically stable. An outpatient clinic visit was planned for the next day, as close as possible to 48 hours after the onset of symptoms. At this visit, the heart rhythm was reassessed on a 12-lead ECG. If atrial fibrillation was still present, patients were referred to the emergency department for delayed cardioversion.

Early cardioversion consisted of pharmacologic cardioversion, preferably with flecainide. Electrical cardioversion was performed in patients with contraindications to pharmacologic cardioversion and in patients with previous or current unsuccessful pharmacologic cardioversion. Patients were

discharged when their condition was determined to be clinically stable.

In patients with a high risk of stroke who had not received previous anticoagulation, such treatment was initiated before or immediately after cardioversion.^{1,12} Transesophageal echocardiography was not performed in any patient. Long-term oral anticoagulation was continued in accordance with the current guidelines based on the patient's score on the CHA₂DS₂-VASc scale.^{1,2,12,13} This scale is used to evaluate the presence of congestive heart failure, hypertension, diabetes, and stroke or transient ischemic attack according to the patient's age and sex, along with the presence of vascular disease, including peripheral arterial disease, previous myocardial infarction, and aortic atheroma. Scores range from 0 to 9, with higher scores indicating greater risk. If complications occurred during emergency department treatments, patients were admitted to the hospital. The need to initiate or intensify drugs for rate and rhythm control was assessed at each contact with patients.

FOLLOW-UP

For all the patients, a visit to the outpatient clinic was scheduled at 4 weeks. The ECG result that was used to assess the primary end point was obtained during this visit. Furthermore, a complete medical history that included a review of symptomatic recurrences, medication use, complications, and hospital admissions was taken. Depending on the availability of devices, patients used ECG telemetry (MyDiagnostick, Applied Biomedical Systems)¹⁴ three times daily or in case of symptoms until the 4-week visit to detect recurrences. (Devices could not be provided to 102 patients because of a lack of availability.) If patients had serious symptoms, they could visit the emergency department or the outpatient clinic. An overview of the trial design is provided in Figure S1 in the Supplementary Appendix.

END POINTS

The primary end point was the presence of sinus rhythm on ECG recorded at the 4-week trial visit. All ECGs were centrally assessed for the presence of sinus rhythm by the first two authors. Secondary end points included the duration of the index visit at the emergency department, emergency department visits related to atrial fibrillation, cardiovascular complications, and time until recurrence

of atrial fibrillation. Cardiovascular complications were defined as events leading to an emergency department visit or hospital admission and included heart failure, ischemic stroke, transient ischemic attack, unstable angina or acute coronary syndrome, symptomatic bradycardia or tachycardia, or hypotension. At the 4-week follow-up visit, we assessed the patients' quality of life using the Atrial Fibrillation Effect on Quality-of-Life questionnaire (AFEQT), with scores ranging from 0 to 100 and higher scores indicating a better quality of life.¹⁵ All secondary end points of the trial are listed in Table S2 in the Supplementary Appendix.

STATISTICAL ANALYSIS

The primary end-point analysis was designed to test whether a wait-and-see approach was noninferior to early cardioversion, as determined by the percentage of patients who were in sinus rhythm at 4 weeks after the index visit. Noninferiority would be shown if the lower limit of the 95% confidence interval for the between-group difference in the primary end point in percentage points was more than -10 (i.e., the difference between the percentage in the delayed-cardioversion group minus the percentage in the early-cardioversion group). This estimation is equivalent to one-sided noninferiority testing with an alpha of 0.025. A noninferiority margin of 10 percentage points was considered acceptable, given the natural variation in the presence of sinus rhythm, the generally low effect of the absence of sinus rhythm on prognosis of the patient, and the availability of good treatment options should treatment be necessary. Using PASS (Power Analysis and Sample Size) software, version 14, we determined that an enrollment of 412 patients would provide a power of 90% to determine noninferiority, assuming that at least 90% of the patients in the two groups had met the primary end point.¹⁶ To allow for attrition, we aimed to enroll 437 patients.

In the primary analysis, we included all the patients who had undergone randomization, except for 10 patients who had withdrawn consent or been lost to follow-up (Fig. 1). We used the method of Farrington and Manning to calculate the 95% confidence interval for the between-group difference in the primary end point.¹⁶ In post hoc sensitivity analyses that included all the patients who had undergone randomization, the results were similar to those in the primary analysis (Table S3 in the Supplementary Appendix).^{17,18}

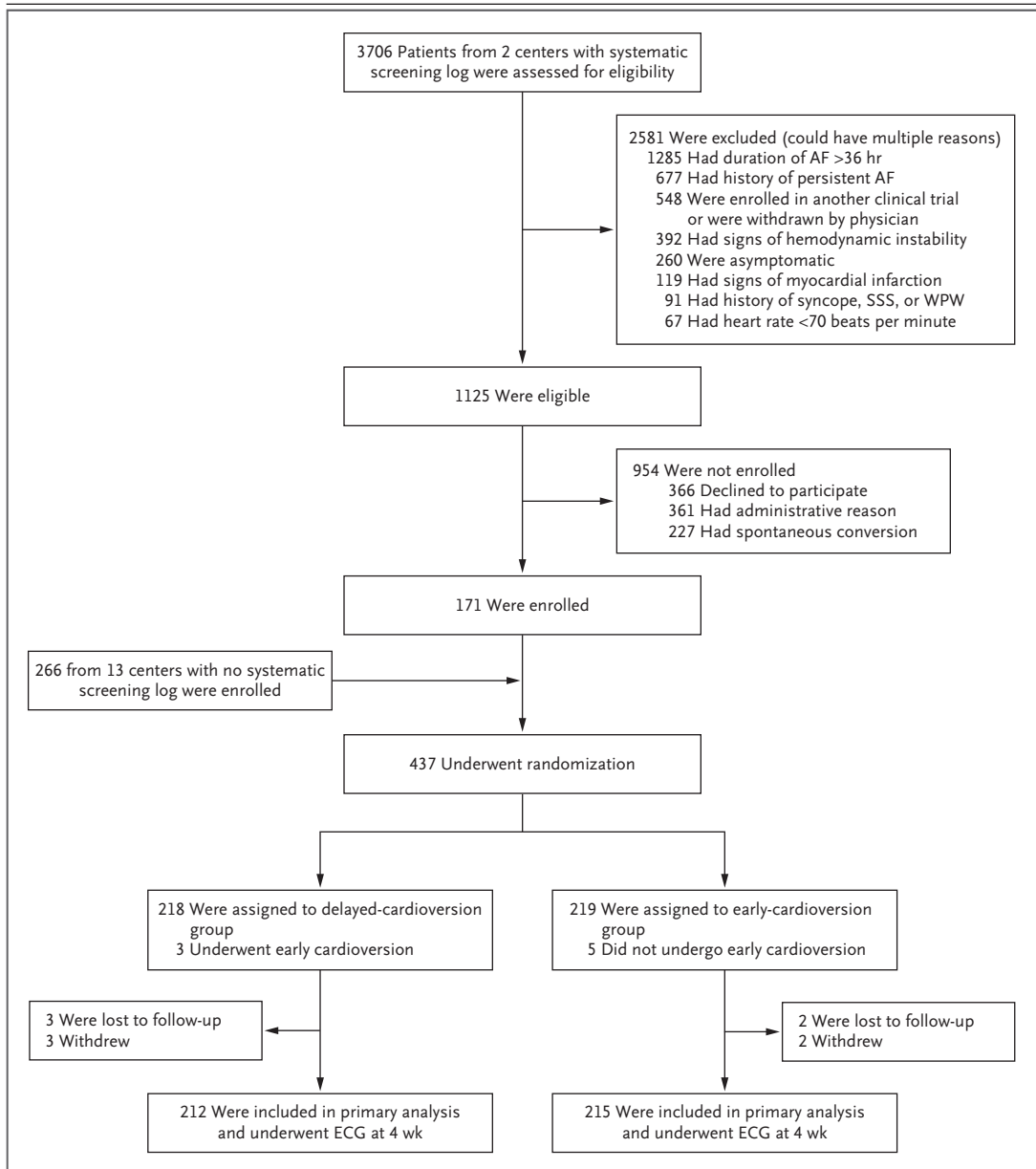


Figure 1. Screening, Randomization, and Follow-up.

In the delayed-cardioversion group, patients received rate-control medication and were discharged when their condition was determined to be clinically stable. An outpatient clinic visit was planned for the next day, as close as possible to 48 hours after the onset of symptoms of atrial fibrillation (AF). At this visit, the heart rhythm was reassessed on 12-lead electrocardiography (ECG). If atrial fibrillation was still present, patients were referred to the emergency department for delayed cardioversion. In the early-cardioversion group, patients underwent immediate pharmacologic or electrical cardioversion, depending on their medical history. SSS denotes sick sinus syndrome, and WPW Wolff–Parkinson–White syndrome.

The time until recurrent atrial fibrillation was analyzed in a subgroup of 335 patients in whom telemetric monitoring had been performed. We performed a Kaplan–Meier analysis to calculate

the time until recurrence of atrial fibrillation and used the Cox proportional-hazards method to calculate hazard ratios with 95% confidence intervals. We used the chi-square test or Fisher’s ex-

act test to compare categorical variables and the independent t-test or the Hodges–Lehmann test to compare continuous variables. There was no prespecified plan to adjust for multiple comparisons. Results for secondary end points are reported with 95% confidence intervals without P values. The calculations were not adjusted for multiple comparisons, and inferences drawn from the intervals may not be reproducible. All statistical analyses were performed with IBM SPSS software, version 25.

RESULTS

PATIENTS

Of the 437 patients who had undergone randomization, 218 were assigned to the delayed-cardioversion group and 219 to the early-cardioversion group (Table 1). The mean (\pm SD) age was 65 ± 11 years; 176 patients (40%) were female, and 192 (44%) had a first episode of atrial fibrillation. Palpitations were the most common symptom (87%), followed by exercise-induced fatigue (26%). An increased risk of stroke, as reflected by a CHA₂DS₂-VAsc score of 2 or higher, was seen in 279 patients (64%). At enrollment, 175 patients (40%) were taking oral anticoagulant drugs, and in 127 patients (29%) anticoagulation was initiated during the index visit (Table S4 in the Supplementary Appendix). The distribution of stroke risk and implementation of anticoagulant therapy are shown in Figure S2 in the Supplementary Appendix.

A screening log was kept in two of the trial centers. Of the 3706 patients who had undergone screening, 2581 (70%) were excluded. The most common reasons for exclusion were a duration of atrial fibrillation of more than 36 hours and a history of persistent atrial fibrillation (Fig. 1).

END POINTS

The primary end point of the presence of sinus rhythm on the ECG recorded at the 4-week visit occurred in 193 of 212 patients (91%) in the delayed-cardioversion group and in 202 of 215 (94%) in the early-cardioversion group (between-group difference, -2.9 percentage points; 95% confidence interval [CI], -8.2 to 2.2 ; $P=0.005$ for non-inferiority) (Fig. 2A).

Almost all the patients were discharged home after the index presentation, with only very few admitted to the hospital (3 patients in the delayed-

cardioversion group and 5 in the early-cardioversion group). Visits to the emergency department because of a recurrence of atrial fibrillation were made by 14 of 212 patients (7%) in the delayed-cardioversion group and in 14 of 215 patients (7%) in the early-cardioversion group.

There were no significant between-group differences with respect to cardiovascular complications (Table 2). Within 4 weeks after randomization (including during the index visit), 10 cardiovascular complications occurred in the delayed-cardioversion group (including 1 patient with ischemic stroke and 3 with acute coronary syndrome or unstable angina) and 8 in the early-cardioversion group (including 1 patient with transient ischemic attack and 3 with acute coronary syndrome or unstable angina). There were no deaths during follow-up. A full list of events is available in Table S6 in the Supplementary Appendix.

The total median duration of the index visit (including delayed cardioversion if necessary) was 120 minutes (range, 60 to 253) in the delayed-cardioversion group and 158 minutes (range, 110 to 228) in the early-cardioversion group. The Hodges–Lehmann estimate for the difference in medians between the two groups was 30 minutes (95% CI, 6 to 51).

Telemetric ECG recordings were available for 335 patients (164 in the delayed-cardioversion group and 171 in the early-cardioversion group). Within 4 weeks after the index visit, a documented recurrence of atrial fibrillation occurred in 49 patients (30%) in the delayed-cardioversion group and in 50 patients (29%) in the early-cardioversion group. The incidence of a first recurrence of atrial fibrillation in a time-to-event analysis was similar in the two groups (hazard ratio in the delayed-cardioversion group, 0.97; 95% CI, 0.65 to 1.43) (Fig. 3). Among the patients who had a recurrence, the median time until the first episode was 12 days (range, 3 to 18) in the delayed-cardioversion group and 8 days (range, 2 to 18) in the early-cardioversion group.

The mean AFEQT global scores were 72 ± 19 in the delayed-cardioversion group and 73 ± 19 in the early-cardioversion group (difference, -1 point; 95% CI, -5.3 to 4.0). The mean scores on the AFEQT subscales were 73 ± 22 and 72 ± 21 , respectively, for symptoms; 70 ± 26 and 69 ± 25 for daily activities; 75 ± 20 and 78 ± 19 for concern about treatment; and 72 ± 24 and 70 ± 26 for satisfaction with treatment.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Delayed Cardioversion (N=218)	Early Cardioversion (N=219)
Age — yr	65±11	65±11
Male sex — no. (%)	131 (60)	130 (59)
Medical history — no. (%)		
Hypertension	118 (54)	133 (61)
Diabetes	21 (10)	25 (11)
Myocardial infarction	24 (11)	13 (6)
Ischemic stroke or transient ischemic attack	12 (6)	15 (7)
CHA ₂ DS ₂ -VASc score — no. (%)†		
0	36 (17)	33 (15)
1	47 (22)	42 (19)
≥2	135 (62)	144 (66)
Symptoms — no. (%)		
Palpitations	188 (86)	193 (88)
Exercise-induced fatigue	55 (25)	60 (27)
Dyspnea	56 (26)	44 (20)
Chest pain	54 (25)	44 (20)
Median heart rate during atrial fibrillation (IQR) — beats/min	123 (101–144)	125 (103–143)
Medication use — no. (%)		
Vitamin K antagonist	34 (16)	34 (16)
Non-vitamin K oral anticoagulant	56 (26)	51 (23)
Antiarrhythmic drug	46 (21)	53 (24)

* Plus-minus values are means ±SD. There were no significant differences between the two groups. Percentages may not total 100 because of rounding. Additional details regarding the baseline characteristics are provided in Table S7 in the Supplementary Appendix. IQR denotes interquartile range.

† The CHA₂DS₂-VASc score is a measure of the risk of stroke in patients with atrial fibrillation, with scores ranging from 0 to 9 and higher scores indicating a greater risk. Congestive heart failure, hypertension, an age of 65 years to 74 years, diabetes, and vascular disease are each assigned one point, and previous stroke or transient ischemic attack and an age of more than 75 years are assigned two points.

TREATMENT

In the delayed-cardioversion group, conversion to sinus rhythm within 48 hours occurred spontaneously in 150 of 218 patients (69%) who were receiving rate-control medication only and in 61 patients (28%) after delayed cardioversion (9 pharmacologic and 52 electrical) (Fig. 2B). Rate-control medication included beta-adrenergic receptor blocking agents (in 155 patients), nondihydropyridine calcium-channel blockers (in 5 patients), digoxin (in 13 patients), or a combination of these drugs (in 1 patient) (Table S5 in the Supplementary Appendix). In 42 patients (19%), rate control was achieved without adding negative dromotropic medication. During the index visit, electrical cardioversion was performed in 2 pa-

tients because of failed rate control in 1 and hypotension in the other. After randomization, 1 patient declined to participate in the wait-and-see approach and underwent pharmacologic cardioversion.

In the early-cardioversion group, conversion to sinus rhythm occurred spontaneously in 36 of 219 patients (16%) before the initiation of the cardioversion and in 171 (78%) after cardioversion (83 pharmacologic and 88 electrical) (Fig. 2B). Rate-control medication was given before cardioversion in 36 patients (Table S5 in the Supplementary Appendix). Early cardioversion was not performed in 5 patients, including 3 who declined cardioversion after randomization, 1 who had acute heart failure during the workup for cardioversion and received

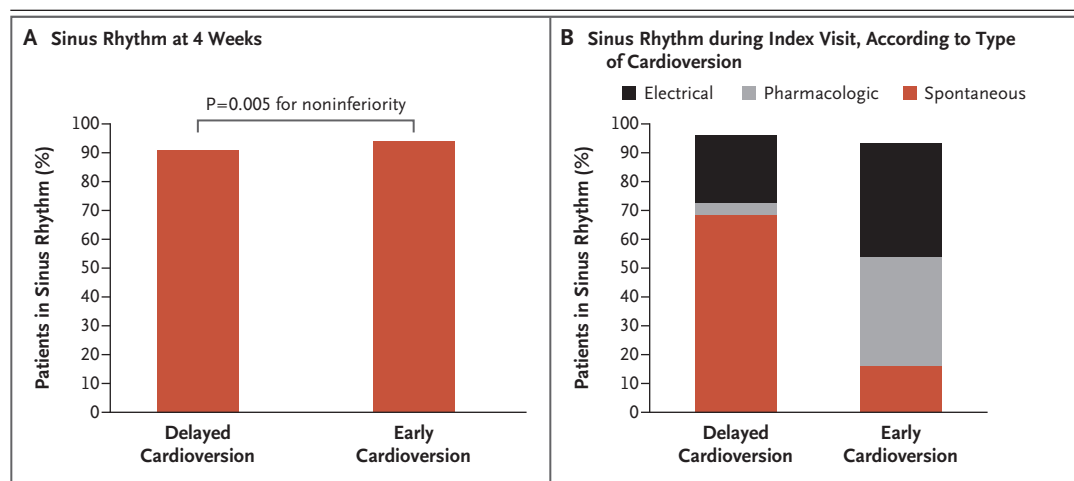


Figure 2. Primary End Point and Distribution of Cardioversion Methods.

Panel A shows the percentage of patients with the primary end point (sinus rhythm at 4 weeks after the index visit) among those who were treated with a wait-and-see approach (delayed-cardioversion group) or early cardioversion. Panel B shows the percentage of patients in sinus rhythm according to the method of cardioversion during the index visit. The index visit included the emergency department visit for all patients and a next-day emergency department visit for delayed cardioversion as needed in the patients who were treated with a wait-and-see approach, all as close as possible to 48 hours after symptom onset. In the delayed-cardioversion group, the rate of spontaneous conversion was higher owing to the wait-and-see period. The spontaneous conversions in the early-cardioversion group occurred during preparation for the cardioversion procedure.

Table 2. Cardiovascular Complications during the Index Visit and during 4 Weeks of Follow-up.

Complication	Index Visit*		During 4 Weeks of Follow-up	
	Delayed Cardioversion (N=218)	Early Cardioversion (N=219)	Delayed Cardioversion (N=218)	Early Cardioversion (N=219)
	<i>number of patients</i>			
Admission for heart failure	1	1	0	0
Ischemic stroke or transient ischemic attack	0	0	1	1
Unstable angina or acute coronary syndrome	0	0	3	3
Bradycardia or hypotension	1 [†]	2	2 [‡]	0
Tachycardia	1	1	1 [§]	0

* The index visit was defined as the initial visit to the emergency department for all patients and included a next-day emergency department visit for delayed cardioversion as needed in the patients who were treated with a wait-and-see approach.

[†] This patient had sinus bradycardia, hypotension, and sinus arrest after delayed cardioversion at 48 hours, which was followed by hospital admission for rhythm observation.

[‡] After the infusion of flecainide, one patient had sinus arrest with asystole for 30 seconds, which necessitated temporary chest compressions until a return of spontaneous circulation.

[§] This patient had wide QRS tachycardia after the infusion of flecainide.

rate-control medication, 1 who underwent successful delayed electrical cardioversion within 48 hours, and 1 who had spontaneous conversion later during the index visit. In the last patient, the attending

physician decided to postpone cardioversion because of skipped doses of non-vitamin K oral anticoagulant medication. The treatments are shown in Figure S3 in the Supplementary Appendix.

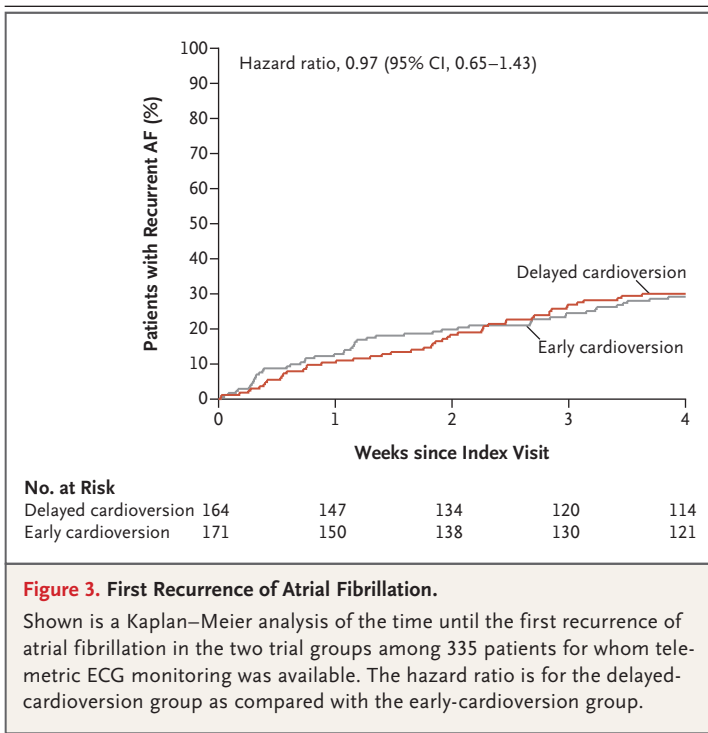


Figure 3. First Recurrence of Atrial Fibrillation.

Shown is a Kaplan–Meier analysis of the time until the first recurrence of atrial fibrillation in the two trial groups among 335 patients for whom telemetric ECG monitoring was available. The hazard ratio is for the delayed-cardioversion group as compared with the early-cardioversion group.

DISCUSSION

Among patients who presented to the emergency department with recent-onset, symptomatic atrial fibrillation, a wait-and-see strategy was noninferior to early cardioversion in obtaining sinus rhythm at 4 weeks after the index visit. Spontaneous conversion frequently occurred in patients in the delayed-cardioversion group and reduced the need for immediate pharmacologic or electrical cardioversion.

The approaches to treating patients with recent-onset atrial fibrillation in the emergency department vary greatly. Early pharmacologic or electrical cardioversion is common practice.¹⁻³ However, the wait-and-see strategy, with delayed cardioversion if needed within 48 hours after symptom onset, has several advantages for patients. First, cardioversion (along with its potential complications) may be avoided. Second, the time spent in the emergency department during the initial presentation may be reduced. Third, spontaneous conversions of atrial fibrillation may be observed, leading to fewer misclassifications of persistent atrial fibrillation.¹⁹ This factor may bear consequences for future rhythm-control strategies, which are considered to be less complex in

patients with paroxysmal atrial fibrillation than in those with persistent atrial fibrillation.^{20,21} Fourth, patients may have the experience that their arrhythmia terminated by itself, which may broaden their insight into treatment options.

In our trial, we found that early cardioversion shortened the time until conversion but did not increase the number of patients who eventually reached sinus rhythm, as compared with the wait-and-see approach. A potential advantage of shortening the time until conversion would be earlier elimination of symptoms and prevention of heart failure, syncope, cardiac or cerebral ischemic events, or progression to persistent atrial fibrillation. However, the wait-and-see strategy yielded similar clinical effects, including symptom control and durable sinus rhythm without signs of progression to persistent atrial fibrillation in almost all the patients. Furthermore, the patients' quality of life was maintained in the delayed-cardioversion group. Delayed cardioversion with longer time spent in atrial fibrillation could promote stroke,²² but timely, guideline-based initiation of anticoagulation^{1,2,12} is expected to reduce the risk of stroke.

Our data suggest that the wait-and-see approach, including a second emergency department visit as needed, is not necessarily more time consuming than early cardioversion. This finding may be due to workup for sedation or drug infusion, waiting time for a sufficient fasting state before electrical cardioversion, or obligatory observation after cardioversion. An unplanned early cardioversion challenges the organization of care in generally overcrowded emergency departments. Pharmacologic cardioversion requires specific expertise in the administration of intravenous antiarrhythmic drugs by the treating cardiologist. Electrical cardioversion requires sedation, involving the expertise of an anesthesiologist. These circumstances may hamper prompt execution of cardioversion, especially since cardioversion in a clinically stable patient is usually not considered to be an emergency procedure. In contrast, almost all the patients in the delayed-cardioversion group could be discharged home after the administration of rate-control medication, regardless of conversion to sinus rhythm.

It cannot be stressed enough that it is mandatory to manage stroke risk appropriately in patients presenting to the emergency department with acute atrial fibrillation, independent of car-

dioversion strategy.²³ In our trial, we stipulated initiation or continuation of appropriate anticoagulation for all high-risk patients. Nevertheless, two patients had a cerebral embolism: one occurred 5 days after spontaneous conversion while the patient was receiving dabigatran initiated at the index visit (score of 2 on the CHA₂DS₂-VASC scale), and the other occurred 10 days after early electrical cardioversion while the patient was receiving rivaroxaban initiated at the index visit (score of 3 on the CHA₂DS₂-VASC scale) (Table S6 in the Supplementary Appendix). Active cardioversion is considered an important trigger for stroke even in patients with recent-onset atrial fibrillation,^{24,25} but spontaneous conversion is also associated with stroke.^{26,27} In this respect, it is important to note that the focus on rate and rhythm control in recent-onset atrial fibrillation may shift physicians' attention away from assessing stroke risk and initiation of antithrombotic treatment in the emergency department, especially in patients undergoing cardioversion.^{28,29} In addition, patients in whom the duration of atrial fibrillation is not known should not be subjected to either of the two strategies that were evaluated in this trial unless they are receiving adequate anticoagulation on a long-term basis or short-term anticoagulation after the exclusion of intraatrial thrombus on transesophageal echocardiography.³⁰

Several limitations of our trial should be men-

tioned. First, the trial was not powered to assess safety, although cardiovascular complications were infrequent in the two groups. Second, the reported incidence of recurrent atrial fibrillation within 4 weeks after randomization was no doubt an underestimation of the true recurrence rate since we used intermittent monitoring. Even so, the 4-week incidence of 30% illustrates the recurrent nature of recent-onset atrial fibrillation. Our finding that there was no significant between-group difference in recurrence rates suggests that the probability of recurrence of atrial fibrillation was not affected by management approach during the acute event.

In conclusion, among patients presenting to the emergency department with recent-onset, symptomatic atrial fibrillation, a wait-and-see approach was noninferior to early cardioversion in achieving sinus rhythm at 4 weeks.

Supported by a grant (837002524) from the Netherlands Organization for Health Research and Development—Health Care Efficiency Research Program and by the Maastricht University Medical Center. Boehringer Ingelheim provided some of the remote monitoring devices.

Dr. Alings reports receiving advisory board fees from Bayer, Bristol-Myers Squibb, Daiichi Sankyo, Boehringer Ingelheim, and Milestone Pharmaceuticals, lecture fees from Pfizer, and grant support from Sanofi. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

The authors' full names and academic degrees are as follows: Nikki A.H.A. Pluymaekers, M.D., Elton A.M.P. Dudink, M.D., Ph.D., Justin G.L.M. Luermans, M.D., Ph.D., Joan G. Meeder, M.D., Ph.D., Timo Lenderink, M.D., Ph.D., Jos Widdershoven, M.D., Ph.D., Jeroen J.J. Bux, M.D., Ph.D., Michiel Rienstra, M.D., Ph.D., Otto Kamp, M.D., Ph.D., Jurren M. Van Opstal, M.D., Ph.D., Marco Alings, M.D., Ph.D., Anton Oomen, M.D., Charles J. Kirchhof, M.D., Ph.D., Vincent F. Van Dijk, M.D., Hemanth Ramanna, M.D., Ph.D., Anho Liem, M.D., Ph.D., Lukas R. Dekker, M.D., Ph.D., Brigitte A.B. Essers, Ph.D., Jan G.P. Tijssen, Ph.D., Isabelle C. Van Gelder, M.D., Ph.D., and Harry J.G.M. Crijns, M.D., Ph.D.

The authors' affiliations are as follows: the Departments of Cardiology (N.A.H.A.P., E.A.M.P.D., J.G.L.M.L., H.J.G.M.C.) and Clinical Epidemiology and Medical Technology Assessment (B.A.B.E.), the Cardiovascular Research Institute Maastricht (N.A.H.A.P., E.A.M.P.D., J.G.L.M.L., H.J.G.M.C.), Maastricht University Medical Center, Maastricht, VieCuri Medical Center Noord-Limburg, Venlo (J.G.M.), Zuyderland Medical Center, Heerlen (T.L.), Elisabeth-TweeSteden Hospital, Tilburg (J.W.), Diaconessen Hospital, Utrecht (J.J.J.B.), University of Groningen, Groningen (M.R., I.C.V.G.), VU University Medical Center Amsterdam (O.K.) and Academic Medical Center (J.G.P.T), Amsterdam, Medical Spectrum Twente, Enschede (J.M.V.O.), Amphia Hospital, Breda (M.A.), Antonius Hospital, Sneek (A.O.), Alrijne Hospital, Leiderdorp (C.J.K.), St. Antonius Hospital, Nieuwegein (V.F.V.D.), Haga Teaching Hospital, The Hague (H.R.), St. Franciscus Gasthuis, Rotterdam (A.L.), and Catharina Hospital, Eindhoven (L.R.D.) — all in the Netherlands.

REFERENCES

1. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014;64(21):e1-e76.
2. 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;37:2893-962.
3. Crijns HJ, Bash LD, Chazelle F, et al. RHYTHM-AF: design of an international registry on cardioversion of atrial fibrillation and characteristics of participating centers. *BMC Cardiovasc Disord* 2012;12:85.
4. 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;31:588-92.
5. Lindberg S, Hansen S, Nielsen T. Spontaneous conversion of first onset atrial fibrillation. *Intern Med J* 2012;42: 1195-9.

6. Geleris P, Stavratsi A, Afthonidis D, Kirpizidis H, Boudoulas H. Spontaneous conversion to sinus rhythm of recent (within 24 hours) atrial fibrillation. *J Cardiol* 2001;37:103-7.
7. Cotter G, Blatt A, Kaluski E, et al. Conversion of recent onset paroxysmal atrial fibrillation to normal sinus rhythm: the effect of no treatment and high-dose amiodarone: a randomized, placebo-controlled study. *Eur Heart J* 1999;20:1833-42.
8. Decker WW, Smars PA, Vaidyanathan L, et al. A prospective, randomized trial of an emergency department observation unit for acute onset atrial fibrillation. *Ann Emerg Med* 2008;52:322-8.
9. Doyle B, Reeves M. "Wait and see" approach to the emergency department cardioversion of acute atrial fibrillation. *Emerg Med Int* 2011;2011:545023.
10. Dudink E, Essers B, Holvoet W, et al. Acute cardioversion vs a wait-and-see approach for recent-onset symptomatic atrial fibrillation in the emergency department: rationale and design of the randomized ACWAS trial. *Am Heart J* 2017; 183:49-53.
11. Van Gelder IC, Groenveld HF, Crijns HJGM, et al. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med* 2010;362:1363-73.
12. European Heart Rhythm Association. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;31:2369-429.
13. 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. *Chest* 2010;137:263-72.
14. Tieleman RG, Plantinga Y, Rinkes D, et al. Validation and clinical use of a novel diagnostic device for screening of atrial fibrillation. *Europace* 2014;16:1291-5.
15. Spertus J, Dorian P, Bubien R, et al. Development and validation of the Atrial Fibrillation Effect on Quality-of-Life (AFEQT) Questionnaire in patients with atrial fibrillation. *Circ Arrhythm Electrophysiol* 2011;4:15-25.
16. Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. *Stat Med* 1990;9:1447-54.
17. Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. *N Engl J Med* 2012; 367:1355-60.
18. Mauri L, D'Agostino RB Sr. Challenges in the design and interpretation of noninferiority trials. *N Engl J Med* 2017; 377:1357-67.
19. Charitos EI, Pürerfellner H, Glotzer TV, Ziegler PD. Clinical classifications of atrial fibrillation poorly reflect its temporal persistence: insights from 1,195 patients continuously monitored with implantable devices. *J Am Coll Cardiol* 2014; 63:2840-8.
20. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Europace* 2018;20(1):e1-e160.
21. Verma A, Jiang C, Betts TR, et al. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med* 2015; 372:1812-22.
22. Nuotio I, Hartikainen JE, Grönberg T, Biancari F, Airaksinen KE. Time to cardioversion for acute atrial fibrillation and thromboembolic complications. *JAMA* 2014;312:647-9.
23. Coll-Vinent B, Martín A, Sánchez J, et al. Benefits of emergency departments' contribution to stroke prophylaxis in atrial fibrillation: the EMERG-AF Study (Emergency Department Stroke Prophylaxis and Guidelines Implementation in Atrial Fibrillation). *Stroke* 2017;48:1344-52.
24. Nieuwlaat R, Dinh T, Olsson SB, et al. Should we abandon the common practice of withholding oral anticoagulation in paroxysmal atrial fibrillation? *Eur Heart J* 2008;29:915-22.
25. Airaksinen KE, Grönberg T, Nuotio I, et al. Thromboembolic complications after cardioversion of acute atrial fibrillation: the FinCV (Finnish CardioVersion) study. *J Am Coll Cardiol* 2013;62:1187-92.
26. Daoud EG, Glotzer TV, Wyse DG, et al. Temporal relationship of atrial tachyarrhythmias, cerebrovascular events, and systemic emboli based on stored device data: a subgroup analysis of TRENDS. *Heart Rhythm* 2011;8:1416-23.
27. Brambatti M, Connolly SJ, Gold MR, et al. Temporal relationship between subclinical atrial fibrillation and embolic events. *Circulation* 2014;129:2094-9.
28. Pisters R, Nieuwlaat R, Prins MH, et al. Clinical correlates of immediate success and outcome at 1-year follow-up of real-world cardioversion of atrial fibrillation: the Euro Heart Survey. *Europace* 2012; 14:666-74.
29. Lip GYH, Gitt AK, Le Heuzey J-Y, et al. Overtreatment and undertreatment with anticoagulation in relation to cardioversion of atrial fibrillation (the RHYTHM-AF study). *Am J Cardiol* 2014;113:480-4.
30. Klein AL, Grimm RA, Murray RD, et al. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med* 2001;344: 1411-20.

Copyright © 2019 Massachusetts Medical Society.

ARTICLE METRICS NOW AVAILABLE

Visit the article page at NEJM.org and click on Metrics to view comprehensive and cumulative article metrics compiled from multiple sources, including Altmetrics. www.nejm.org/about-nejm/article-metrics.