Cardioversion of atrial fibrillation revisited

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Proefschrift

Ter verkrijging van de graad van doctor aan de Universiteit van Maastricht, op gezag van de Rector Magnificus, Prof. dr. Pamela Habibović volgens het besluit van het College van Decanen, in het openbaar te verdedigen op
vrijdag 23 september 2022 om 10:00 uur

door

Nikki Agnes Harry Anne Pluymaekers
Geboren op 31 oktober 1989
te Maastricht

Promotor
Prof. dr. H.J.G.M. Crijns

Copromotoren
Dr. J.G.L.M. Luermans
Dr. D.K. Linz

Beoordelingscommissie
Prof. dr. P.G.A. Volders (voorzitter)
Prof. dr. H.P. Brunner-La Rocca
Prof. dr. A.J. Camm
Prof. dr. J. Healey
Prof. dr. F.W. Prinzen

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.
Further financial support by FibriCheck is greatly appreciated.

Cover design by: M. Mafi Rad
Layout and Graphic Design by: M. Mafi Rad

Printed by: Gildeprint

ISBN: 978-94-6419-558-3

Voor mijn familie

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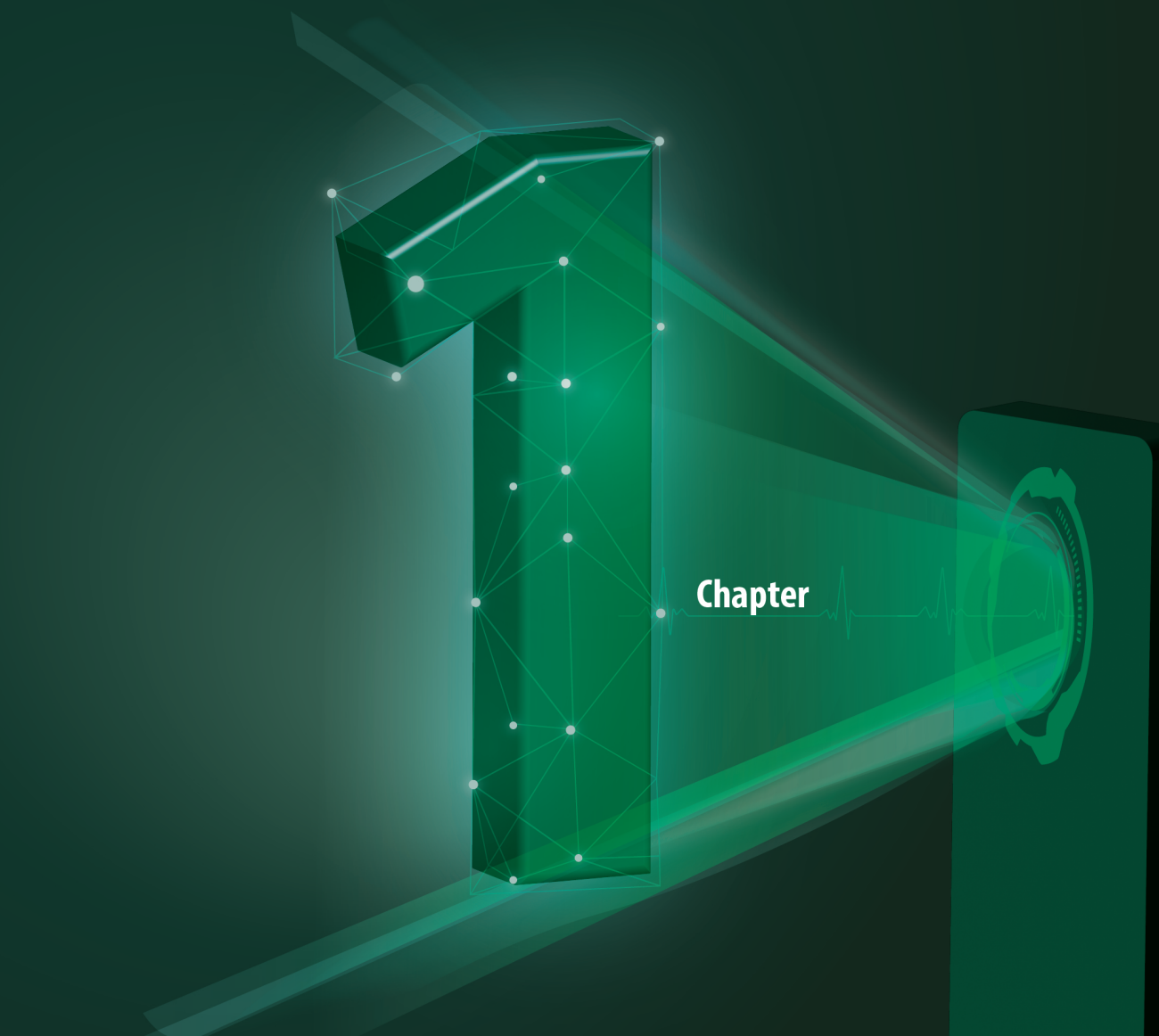


DEFINITION AND DIAGNOSIS OF ATRIAL FIBRILLATION

Atrial fibrillation (AF) is an arrhythmia characterized by uncoordinated atrial electrical activation, followed by an irregular and often rapid ventricular contraction[1]. A 12-lead electrocardiogram (ECG) or a single lead ECG tracing of more than 30 seconds with absence of p-waves and an irregular ventricular rate confirms the diagnosis of AF[2]. This was first recorded in humans in 1909 by Lewis[3]. Currently, AF is the most commonly encountered arrhythmia in adults worldwide[2] and causes a significant health care burden[4-6]. Despite the high prevalence and the enormous advances in understanding the pathophysiology, the exact pathogenesis is still not clearly understood. The prevailing concept presents an interaction between initiating triggers, mostly originating from one or more pulmonary veins, and an atrial substrate capable of maintaining the arrhythmia[7-9]. This concept forms the basis for the classification and management strategies of AF.

TYPE OF AF

Different types of AF have been described mainly based on the duration of AF and symptoms. First of all, there is a differentiation between asymptomatic and symptomatic AF. Patients can present with symptoms such as palpitations, dyspnoea, chest pain, dizziness or are asymptomatic. Around 30-40% of AF patients do not report any symptoms [10,11]. The proportion of asymptomatic AF is probably an underestimation since a lot of asymptomatic individuals with AF remain undiagnosed. And even in the large proportion of patients with AF who report symptoms, it often remains challenging to distinguish between symptoms directly related to AF (AF-symptoms in patients) compared to symptoms related to concomitant conditions and risk factors (symptoms in AF patients). The determination of the temporal relationship between symptoms and rhythm can help to assess symptom-rhythm correlation. Despite the potential clinical implications on the management of AF, the best approach how to assess this symptom-rhythm correlation remains unclear.

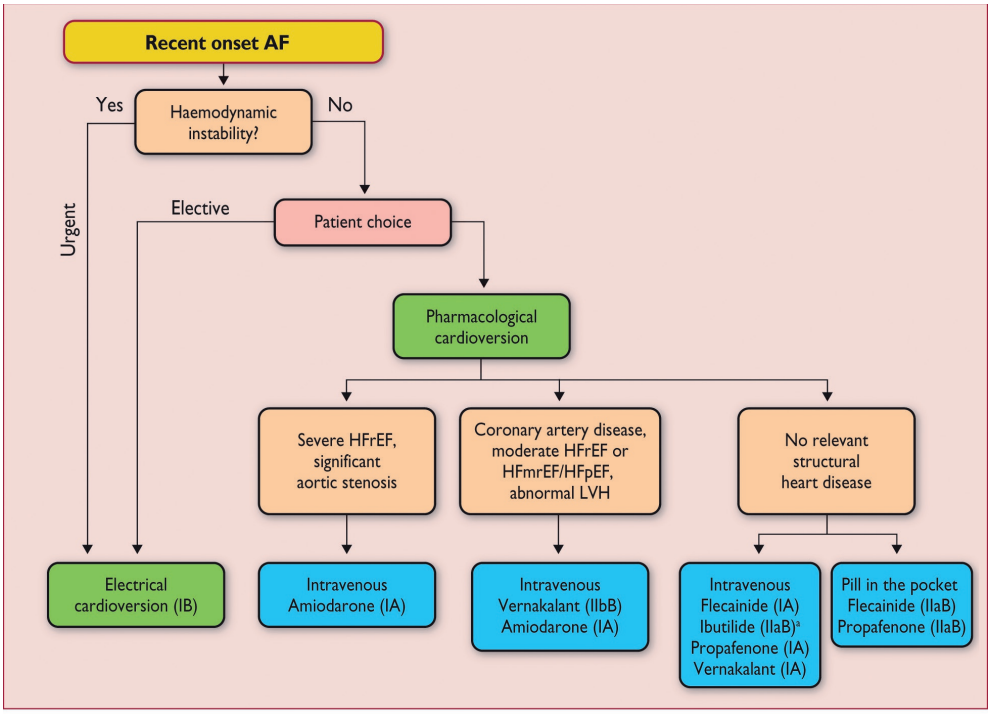
Additionally, AF can also be classified based on the duration of episodes and the way how the episodes terminate[12]. The European Society of Cardiology (ESC) guidelines distinguish five types of AF: 1) First detected AF is the first diagnosis of AF irrespective of the duration, symptoms or conversion method. 2) Paroxysmal AF is defined as self-terminating AF within 7 days; 3) Persistent AF is defined as AF lasting longer than 7 days, including episodes requiring cardioversion for termination > 7 days. 4) Long-standing persistent AF is persistent AF lasting >1 year in which a rhythm control strategy is adopted; 5) Permanent AF, in which the AF is accepted and no rhythm control is achieved[2].

Clinically, the differentiation between paroxysmal AF and persistent AF can be difficult. Patients with AF for 7 or more days can still terminate spontaneously. Despite variation in time to self-termination, there can also be variation over time within one patient since paroxysmal AF can progress to persistent or permanent AF. Progression may occur in 1-15% of the general AF population annually depending on definition of progression[13,14] and reduces the health related quality of life[15]. Additionally, the rate of AF progression is dependent on the presence of specific individual risk factors [14,16] and the number of concomitant risk factors[17].

MANAGEMENT OF AF

Management of AF focuses on alleviation of symptoms and prevention of serious adverse events, since patients with AF have an increased risk of concomitant diseases such as stroke[18], coronary artery disease[19] and heart failure[20]. Therefore, a comprehensive approach is required based on the AF Better Care (ABC) pathway[2]. The first part of this pathway 'A' (anticoagulation/avoid stroke) focuses primarily on installing appropriate anticoagulation therapy according to the stroke risk based on the CHA_2DS_2-VASc score[18] . The second part 'B' stands for better symptom management.

To alleviate symptoms rate or rhythm control treatment can be initiated or adapted. A rate control strategy primarily focuses on symptom relief by reducing the ventricular heart rate with rate control drugs such as beta-blockers, non-dihydropyridine calcium-channel blockers or digoxin. In contrast, rhythm control can be achieved by antiarrhythmic drugs (AAD), electrical cardioversion (ECV) and/or catheter based or surgical ablation procedures and focuses on maintaining sinus rhythm. The choice between rate or rhythm control has been under debate for the last decades. For many years the aim was maintaining sinus rhythm, however the frequent recurrences of AF and the adverse effects of rhythm control had led to question this approach. In 2002 two landmark trials comparing rate and rhythm control were published. In the AFFIRM trial, Wyse et.al.[21] randomized elderly patients with AF and at high risk for stroke or death to a rhythm control strategy (AAD and ECV if necessary) or rate control strategy (beta-blockers, calcium-channel blockers or digoxin) and showed no significance difference between the two strategies concerning overall mortality. Although not statistically significant, there was a trend towards a survival benefit with the rate control strategy[21]. In the RACE trial, Van Gelder et.al.[22] randomized patients with recurrent persistent AF to a rhythm control strategy (serial electrical cardioversion and AAD) or a rate control strategy (beta-blockers, non-dihydropyridine calcium-channel blockers, digoxin or a combination). The primary endpoint was a composite of death from cardiovascular causes, heart failure, thrombo-embolic complications, bleeding, the need for a pacemaker, or severe adverse effects of antiarrhythmic drugs. This non-inferiority trial showed no difference between rate or rhythm control concerning the primary outcome[23]. Those two trials showed that rate control was an acceptable strategy for elderly patients and patients with recurrent persistent AF. Especially since also in terms of improvement of AF related symptoms both strategies yield similar clinical effect for patients with persistent AF[24]. Furthermore, in a subgroup of patients with heart failure with reduced left ventricular ejection fraction and AF, there was no benefit from a rhythm control strategy compared to rate control[25]. Recently, in the EAST-AFNET 4 trial Kirchhof et.al. included patients with 'early' AF (<12months of first diagnosis, median duration of AF 36 days) and randomized patients to early rhythm control (AAD, ECV and/or AF ablation) or usual care (initial rate control, in case of uncontrolled symptoms rhythm control was allowed). This trial showed a beneficial effect of installing early chronic rhythm control in terms of cardiovascular outcome (primary endpoint) in patients with early AF[26]. Note that one third of patients in EAST were asymptomatic with their AF. Patients with recent-onset AF (<48hours) who present at the emergency department were not included in the above mentioned trials. In those patients with recent-onset symptomatic AF who present at the emergency department, immediate restoration of sinus rhythm by pharmacological cardioversion (PCV) or ECV is frequently performed[27-29] and recommended by the 2016 and 2020 ESC guidelines on the management of AF[2,30] (figure 1). However, as we discussed before, paroxysmal AF episodes are self-terminating, usually within 7 days. Unfortunately, the mechanism of spontaneous conversion is still not fully understood[31-34] as it could improve clinical cardioversion. On the other hand, it could be questioned whether immediate restoration by means of cardioversion is always necessary since symptoms can also be alleviated by rate control medication. This question of rate or rhythm control for (acute) recent-onset AF, and whether we should revisit the current cardioversion practices will have a central role in this thesis (Chapter 4).



AF = atrial fibrillation; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVH = left ventricular hypertrophy.
[a]Ibutilide should not be used in patients with long QT interval.

Figure 1. *Rhythm control management of recent-onset AF. Kirchhof P, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893-962, reprinted with permission of Oxford University Press.*

The third part 'C' consists of cardiovascular risk factors and comorbidity optimization. This includes the assessment and management of concomitant cardiac conditions and risk factors that predispose to AF, such as: hypertension, heart failure, diabetes mellitus, myocardial infarction, obstructive sleep apnoea, chronic obstructive pulmonary disease, smoking, obesity, thyroid dysfunction and excessive alcohol consumption[30,35-39]. Several large trials have shown that lifestyle and risk factor modifications increase AF-free survival[40-44]. For instance, Voskoboinik and colleagues recently reported that abstinence of alcohol reduces the recurrent rate of AF in regular drinkers (53% vs. 73%) [44]. Pathak and colleagues compared in the ARREST-AF trial (Aggressive Risk Factor Reduction Study) an aggressive risk factor management which consisted of blood pressure control, weight management, lipid management, glycaemic control, obstructive sleep apnoea treatment, smoking cessation and alcohol reduction to usual care. This trial showed a reduction of AF recurrence after catheter ablation for AF in the aggressive risk factor management group[41]. Also in patients with persistent AF and heart failure, targeted therapy of underlying conditions improved maintenance of sinus rhythm[43]. All this strengthened strict control of risk factors as an integral part of the rhythm and rate control strategies, gaining a class I recommendation in the ESC guidelines on the management of AF[2,30]. Note that part 'C' may have a significant impact on effectiveness of part 'B' since reducing the impact of associated conditions if not reducing symptoms directly related to AF (AF-symptoms in patients) it certainly will ameliorate symptoms related to concomitant conditions and risk factors (symptoms in AF patients).

AIM AND OUTLINE OF THIS THESIS

The main aim of this thesis is to revisit current cardioversion practices for atrial fibrillation.

Part I. Pre-cardioversion for AF

Part I of this thesis focuses on the time period just before a cardioversion. One of our observations was that many patients present to the emergency department with symptomatic recent-onset AF and have spontaneous conversion at the emergency department before an active cardioversion could be performed. This triggered us to investigate which patients had the highest likelihood of spontaneous conversion, the results of this study are presented in ***chapter 2*** of this thesis. ***Chapter 3*** provides a systematic review concerning spontaneous conversion of AF at the emergency department. The hypothesis generated from this clinical experience (that most patients will have spontaneous conversion to sinus rhythm) led to a multicentre randomized controlled trial[45] which will be discussed in part II of this thesis.

Part II. Cardioversion of AF

Part II of this thesis focuses on cardioversion for recent-onset AF. ***Chapter 4*** reports the results of the multicentre randomized controlled trial in which a wait-and-see approach with delayed cardioversion is compared to the current standard of care of early cardioversion (the RACE 7 ACWAS trial). As mentioned above, in patients with recent-onset AF their arrhythmia often terminates spontaneously[4,46,47]. An alternative approach to acute restoration by PCV or ECV could be a wait-and-see approach which may avoid hospitalization and overtreatment. This wait-and-see approach consists of administration of rate-control medication and delayed cardioversion <48hours of symptom onset only if necessary, allowing for spontaneous conversion. The hypothesis of this trial was to see whether a wait-and-see approach was non-inferior to acute cardioversion in terms of obtaining durable sinus rhythm at 4 weeks follow-up. The results of this trial are included in the 2020 ESC guidelines on the management of AF. In ***Chapter 5 and 6*** the accompanying editorial and letter to the editor concerning this trial are presented. Subsequently, ***chapter 7*** summarizes the one-year clinical outcome and cost-effectiveness of this trial. One of the hypotheses was that a wait-and-see approach would reduce health care costs by preventing overtreatment, even more so since most patients have recurrent episodes of AF burdening the health care system and impacting on long-term health related costs.

Part III. Follow-up after cardioversion

Part III focuses on the management after a cardioversion of AF has been performed. ***Chapter 8*** presents the results of a retrospective study which evaluates the safety of elective external cardioversion in patients with contemporary cardiac implantable electronic devices (CIEDs) and assesses the need for immediate device interrogation after electrical cardioversion. The safety concern of ECV in CIEDs is mainly based on older reports describing lead and/or device malfunction caused by for instance energy shunting from the device to unipolar leads or paddle positions close to the pulse generator, although nowadays the use of biphasic shock waveforms for ECV allows reduction of the applied amount of energy and also the use of bipolar leads seems to reduce the risk. In ***Chapter 9*** we discuss the "symptom-rhythm" correlation peri-cardioversion. This correlation may have important implications for planning rhythm control. As we noticed in clinical care, it may be quite difficult to assess the correlation between self-reported symptoms and the heart rhythm. We reasoned that a planned cardioversion would be ideal to evaluate this symptom-rhythm correlation since it provides a before-after comparison ("diagnostic cardioversion"). The results of this observational study are presented in ***Chapter 9.***

Part IV. Perspectives in cardioversion for AF

Part IV presents some of the future perspectives and challenges in cardioversion for AF. As shown in this thesis spontaneous conversion to normal sinus rhythm occurs in almost 70% of patients with recent-onset AF by simply applying rate control (wait-and-see approach). But the remaining question is still whether cardioversion is needed at all in patients with recent-onset AF. Waiting for spontaneous conversion even after 48 hours may further obviate the need for cardioversion, and thereby improve resource utilization in the emergency departments, and reduce costs. We introduce this approach of extended rate control in patients with recent-onset AF as a "watchful-waiting" approach. It consists of symptom control by optimal rate control during the first 4 weeks after onset of AF and an elective cardioversion at four weeks if AF does not convert spontaneously. To allow a safe watchful-waiting approach, a remote rate and rhythm monitoring infrastructure is required to allow instantaneous treatment decisions. In the last decade several wearable devices and mobile-health (mHealth) solutions for the diagnosis and management of AF emerged, but no specific mHealth infrastructure was developed which is still preventing wider implementation in the clinic[48]. In the RACE 7 ACWAS study (**Chapter 4**) and the observational study in **Chapter 9** we used stand-alone mHealth applications for AF monitoring. Unfortunately, these monitoring data could not be assessed remotely which prevented instantaneous treatment decisions. We used this initial experience to develop a new device-based telemonitoring infrastructure for remote rate and rhythm control for patients with recent-onset AF which is currently used in the on-going RACE 9 Observe AF trial (ClinicalTrials.gov NCT04612335). This specific system allows for immediate interaction with the patients on rate, rhythm and symptoms. The implementation of the new device-based rate and rhythm monitoring infrastructure was significantly accelerated by the COVID-19 pandemic which an overall triggered mHealth use in many Cardiology clinics[49]. Due to social distancing measures and government restrictions all face-to-face consultations in our AF clinic were changed to teleconsultations. The latter consultations lack information on rate or rhythm of the patient making these telephone contacts less effective. In the Maastricht University Medical Center, we developed a new mHealth infrastructure – similar to the above - to allow remote rate and rhythm monitoring for all AF patients. Considering the hygienic concerns of the use of a device during COVID-19, the infrastructure was expanded to a mobile phone app on the smartphone of the patients. This approach called the TeleCheck-AF approach is a remote on-demand and on-prescription monitoring infrastructure, which is based on a mobile phone app using photoplethysmography (PPG) technology allowing rate and rhythm monitoring around teleconsultations. In ***Chapter 10*** we describe the results of the first thirty patients and the implementation of the TeleCheck-AF approach in Europe in ***Chapter 11***. The outline of Chapter 11 was used to rapidly and successfully spread this TeleCheck-AF approach to 40 hospitals in Europe. This new infrastructure containing a device based and mobile app based possibility for remote rate and rhythm assessment can help the implementation of the delayed cardioversion approach for recent-onset AF since it allows not only assessment of the rate and rhythm remotely but also enables instantaneous treatment decisions. This approach is described in the last chapter of part IV ***(Chapter 12)***, and shows the implementation of our revisited cardioversion practices (RACE 7 ACWAS) for recent-onset AF combined with the new mHealth telemonitoring infrastructure. This thesis ends with a general discussion ***(Chapter 13)***.

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PART I

Pre-cardioversion for AF

N.A.H.A. Pluymaekers, E.A.M.P. Dudink, B. Weijs, K. Vernooy, D.E.J. Hartgerink, J.S. Jacobs, Ö. Erküner, N. Marcks, Y.J.M. van Cauteren, T. Dinh, R.M.A. ter Bekke, J.W.E.M.W Sels, T.S.R. Delnoij, Z. Geyik, R.G.H. Driessen, D.W. den Uijl, H.J.G.M. Crijns, J.G.L.M. Luermans.

Netherlands Heart Journal 2021;29:255-61.

Clinical determinants of early spontaneous conversion to sinus rhythm in patients with atrial fibrillation

ABSTRACT

Background

The current standard of care for acute atrial fibrillation (AF) focuses primarily on immediate restoration of sinus rhythm by cardioversion, although AF often terminates spontaneously.

Objective

To identify determinants of early spontaneous conversion (SCV) in patients presenting at the emergency department (ED) because of AF.

Methods

An observational study was performed of patients who visited the ED with documented AF between July 2014 and December 2016. The clinical characteristics and demographics of patients with and without SCV were compared.

Results

We enrolled 943 patients (age 69±12 years, 47% female). SCV occurred within 3 h of presentation in 158 patients (16.8%). Logistic regression analysis showed that duration of AF <24 h [odds ratio (OR) 7.7, 95% confidence interval (CI) 3.5-17.2, $p<0.001$], left atrial volume index <42 ml/m^2 (OR 1.8, 95% CI 1.2-2.8, $p=0.010$), symptoms of near-collapse at presentation (OR 2.4, 95% CI 1.2-5.1, $p=0.018$), a lower body mass index (BMI) (OR 0.9, 95% CI 0.91-0.99, $p=0.028$), a longer QTc time during AF (OR 1.01, 95% CI 1.0-1.02, $p=0.002$) and first-detected AF (OR 2.5, 95% CI 1.6-3.9, $p<0.001$) were independent determinants of early SCV.

Conclusion

Early spontaneous conversion of acute AF occurs in almost one-sixth of admitted patients during a short initial observation in the ED. Spontaneous conversion is most likely to occur in patients with first-onset, short-duration AF episodes, lower BMI, and normal left atrial size.

Keywords

Acute atrial fibrillation, spontaneous conversion, determinants, treatment, cardioversion, wait-and-see approach.

INTRODUCTION

Atrial fibrillation (AF) is a commonly encountered arrhythmia and causes a significant health care burden [1,2]. The prevalence of AF, and thereby the economic costs (mainly for hospitalisation and treatment), continues to increase [3,4]. Current treatment is focused primarily on appropriate anticoagulation, rate or rhythm control strategy, and the assessment of underlying conditions that predispose to AF. In patients with acute symptomatic AF, the primary aim of treatment is early restoration of sinus rhythm (SR) by pharmacological cardioversion (PCV), electrical cardioversion (ECV) or a combination of both [4]. However, it could be questioned whether immediate restoration by means of cardioversion is necessary, since several previous studies have reported that spontaneous conversion (SCV) of AF to SR occurs in up to 70% of acute AF cases [1,5-9], making prompt ECV or PCV unnecessary. Appropriate identification of patients with a high likelihood of SCV of AF is needed. The aim of this study is to determine the clinical characteristics associated with early SCV in patients presenting with AF at the emergency department (ED).

METHODS

Setting

We conducted an observational study of 943 adult patients who visited the ED with AF between July 2014 and December 2016. Patients were included at the Maastricht University Medical Centre+ (MUMC+). The study was approved by the Institutional Review Board of the MUMC+.

Study population

All patients were aged over 18 years. The patients either had electrocardiographic documentation of AF at presentation or were patients with pre-hospital conversion if they had previous electrocardiographically documented AF with a verified symptom-rhythm correlation or if the current episode was electrocardiographically documented by the general practitioner and patients converted on their way to the hospital. For the purpose of this study the following exclusion criteria were applied: a history of persistent or permanent AF, haemodynamic instability, or signs of acute coronary syndrome or heart failure at initial work-up. Patients were treated at the discretion of the treating physician; no additional study-related action was taken. The institutional protocol allowed for both forms of cardioversion, depending on patients' profiles, timing of eventual cardioversion in relation to last meal, and physicians' preferences and experiences.

Data collection

Baseline characteristics were collected, including age, sex, duration of AF, current symptoms, medical history, and (prior) echocardiographic data. Patients underwent a full physical examination, a 12-lead electrocardiogram analysed with software from the MUSE system (MUSE®, GE Medical Systems, Milwaukee, US), and laboratory investigation at the ED. Information regarding therapeutic strategy including rate versus rhythm control was noted. We compared characteristics between patients with SCV and non-spontaneous conversion (non-SCV).

Definitions

For the purpose of this study patients with a history of persistent or permanent AF, defined as a previous episode of AF lasting longer than >48 h, were excluded. The duration of the current episode was not an exclusion criterion; therefore episodes longer than 48 h were also included if the patient had no history of persistent or permanent AF. Conversion was defined as spontaneous if the patient converted to SR without active cardioversion, either ECV or PCV, before presentation at the ED or within 3 h after ED presentation, which was the time interval allowing proper work-up towards active cardioversion and during which spontaneous cardioversion could happen.

Statistical analysis

Data management and analysis were performed using IBM SPSS version 25, Armonk, NY. Results were reported as mean ± standard deviation or median with interquartile range (IQR). A chi-square or Fisher's exact test was used to compare categorical variables. Normally distributed continuous covariates were compared using the Student's *t*-test. For comparison of skewed continuous covariates the Mann-Whitney U test was used. A binary logistic regression was performed, using backward selection until all variables in the model reached a *p*-value <0.05, to identify possible determinants for SCV. All variables showing a significant ($p<0.05$) univariable relationship for SCV were included in the regression analysis. A *p*-value of <0.05 was considered statistically significant

RESULTS

We enrolled 943 consecutive patients (Fig. 1) with a mean age of 69±12 years, 47% females. Expressed symptoms at presentation were palpitations in 74% of patients, dyspnoea in 28%, chest pain in 20%, dizziness in 16%, fatigue in 8%, near-collapse in 7%, and 10% experienced other symptoms of AF. An overview of the baseline characteristics of SCV and non-SCV patients is presented in Table 1.

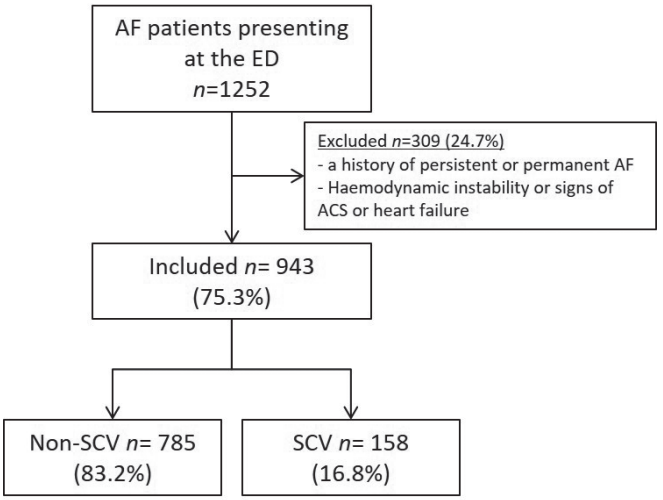

Figure 1. Study flow chart. *Exclusion criteria were a history of persistent or permanent atrial fibrillation **(AF)**, haemodynamic instability, or signs of acute coronary syndrome **(ACS)** or heart failure at presentation. Persistent AF was defined for this trial as a previous episode lasting longer than 48 h. Haemodynamic instability was defined as a heart rate above 170 bpm or a systolic blood pressure below 100 mmHg. **ED** emergency department, **SCV** spontaneous conversion.*

Table 1. **Baseline characteristics according to spontaneous cardioversion.**

Total, *n*=943	**Non-SCV *n*=785 (83.2%)**		**SCV *n*=158 (16.8%)**		***p*-value (non-SCV vs SCV)**
Demographics					
Age, years (±SD)	68.5	(±12.6)	69.7	(±11.3)	0.257
Female, *n* (%)	361	(46.0%)	85	(53.8%)	0.073
BMI, kg/m^2 (±SD)	28.5	(±6.5)	27.0	(±4.6)	0.001
History					
Hypertension, *n* (%)	475	(60.5%)	107	(67.7%)	0.089
Diabetes mellitus, *n* (%)	101	(12.9%)	23	(14.6%)	0.566
Hypercholesterolaemia, *n* (%)	285	(36.3%)	41	(25.9%)	0.013
Smoking:					
- Current, *n* (%)	87	(11.1%)	16	(10.1%)	0.725
- Past, *n* (%)	69	(8.8%)	12	(7.6%)	0.625
Myocardial infarction, *n* (%)	90	(11.5%)	18	(11.4%)	0.979
Coronary artery disease, *n* (%)	140	(17.8%)	27	(17.1%)	0.823
Percutaneous coronary intervention, *n* (%)	81	(10.3%)	16	(10.2%)	0.962
Coronary artery bypass graft, *n* (%)	59	(7.5%)	3	(1.9%)	0.009
Valve surgery, *n* (%)	42	(5.6%)	4	(1.3%)	0.021
Stroke					
- Ischaemic, *n* (%)	36	(4.6%)	3	(1.9%)	0.122
- Haemorrhagic, *n* (%)	0	(0%)	1	(0.6%)	0.168
Transient ischaemic attack, *n* (%)	31	(3.9%)	9	(5.7%)	0.320
Pulmonary embolism, *n* (%)	8	(1.0%)	1	(0.6%)	>0.999
Deep venous thrombosis, *n* (%)	2	(0.2%)	3	(1.9%)	0.036
Congenital heart disease, *n* (%)	10	(1.3%)	2	(1.3%)	>0.999
Hyperthyroidism, *n* (%)	18	(2.3%)	7	(4.4%)	0.168
Hypothyroidism, *n* (%)	19	(2.4%)	5	(3.2%)	0.588
Chronic obstructive pulmonary disease, *n* (%)	30	(3.8%)	1	(0.6%)	0.040
Peripheral artery disease, *n* (%)	26	(3.3%)	7	(4.4%)	0.485
Obstructive sleep apnoea syndrome, *n* (%)	18	(2.3%)	5	(3.2%)	0.569
Atrial flutter, *n* (%)	89	(11.3%)	23	(14.6%)	0.254
ICD, *n* (%)	29	(3.7%)	2	(1.2%)	0.118
PM, *n* (%)	20	(2.5%)	4	(2.5%)	>0.999
Ablation therapy for AF, *n* (%)	87	(11.1%)	12	(7.6%)	0.192
CHA_2DS_2-VASc (±SD)	2.6	(±1.6)	2.7	(±1.5)	0.370
Medication at baseline					
Vitamin K antagonist, *n* (%)	281	(35.8%)	41	(25.9%)	0.017
Direct oral coagulants, *n* (%)	144	(18.3%)	32	(20.3%)	0.574
Other medication					
Acetylsalicylic acid, *n* (%)	88	(11.2%)	23	(14.6%)	0.234
ACE inhibitors, *n* (%)	142	(18.1%)	27	(17.1%)	0.765
ARB, *n* (%)	246	(31.3%)	50	(31.8%)	0.900

Table 1. (continued)

Total, *n*=943	**Non-SCV *n*=785 (83.2%)**		**SCV *n*=158 (16.8%)**		***p*-value (non-SCV vs SCV)**
Spironolactone, *n* (%)	19	(2.4%)	2	(1.3%)	0.556
Beta-blocker, *n* (%)	353	(45.0%)	68	(43.0%)	0.656
Digoxin, *n* (%)	37	(4.7%)	5	(3.2%)	0.388
AAD use, *n* (%)	231	(29.4%)	39	(24.7%)	0.229
Statin, *n* (%)	303	(38.6%)	56	(35.4%)	0.449
Echocardiography[a]					
LAV index <42 ml/ m^2, *n* (%)	317	(47.8%)	84	(61.3%)	0.004
Normal RAV index ml/m^2, *n* (%)	258	(32.9%)	66	(41.8%)	0.031
LVH, *n* (%)	248	(31.6%)	47	(29.7%)	0.648
LVEF (±SD)	59.5	(±7.5)	61.6	(±5.0)	0.002
AF characteristics					
First-detected AF, *n* (%)	251	(32.0%)	66	(41.8%)	0.017
Duration of symptoms <24 h, *n* (%)	534	(68.0%)	143	(90.5%)	<0.001
Mean systolic blood pressure, mmHg (±SD)	135.0	(±20.4)	134.2	(±26.2)	0.735
Mean diastolic blood pressure, mmHg (±SD)	85.0	(±15.1)	82.2	(±14.9)	0.044
Palpitations, *n* (%)	565	(72.0%)	129	(81.6%)	0.012
Dyspnoea, *n* (%)	232	(29.6%)	28	(17.7%)	0.002
Fatigue, *n* (%)	72	(9.2%)	5	(3.2%)	0.064
Near-collapse, *n* (%)	48	(6.1%)	18	(11.4%)	0.018
Chest pain, *n* (%)	146	(18.6%)	44	(27.8%)	0.008
Dizziness, *n* (%)	117	(14.9%)	32	(20.3%)	0.093
Other symptoms of AF, *n* (%)	79	(10.1%)	16	(10.1%)	0.981
ECG					
Heart rate, bpm (±SD)	118	(±27)	125	(±29)	0.004
QRS duration, ms (±SD)	94	(±21)	96	(±25)	0.356
LBBB, *n* (%)	21	(2.7%)	6	(4.7%)	0.260
QTc, ms (±SD)	452	(±34)	460	(±34)	0.035
Laboratory results					
Potassium, mmol/l (*n*=877) (±SD)	4.2	(±0.5)	4.2	(±0.6)	0.277
Creatinine, umol/l (*n*=578) (±SD)	95.3	(±42.7)	104.7	(±103.4)	0.142
Haemoglobin, mmol/l (*n*=423) (±SD)	8.6	(±1.1)	8.4	(±1.2)	0.094
TSH, mU/l (*n*=516) (±SD)	2.6	(±5.9)	2.9	(±3.6)	0.602

[a] *Based on n=854 due to missing data. Normal RAV index for men 25±7 ml/m^2, women 21±6 ml/m^2*

AAD *antiarrhythmic drug,* ***ACE*** *angiotensin-converting enzyme,* ***AF*** *atrial fibrillation,* ***ARB*** *angiotensin receptor blockers, BMI body mass index,* ***CI*** *confidence interval,* ***ECG*** *electrocardiography,* ***ICD*** *implantable cardioverter-defibrillator,* ***LAV*** *left atrial volume,* ***LBBB*** *left bundle branch block,* ***LVEF*** *left ventricular ejection fraction,* ***LVH*** *left ventricular hypertrophy (>9 mm),* ***PM*** *pacemaker,* ***RAV*** *right atrial volume,* ***SCV*** *spontaneous conversion,* ***TSH*** *thyroid-stimulating hormone.*

The median time interval of echocardiogram was -3 weeks (range -28 months to 74 months).

Cardioversion

Spontaneous conversion to SR occurred in 158 (16.8%) patients. In patients without SCV, an active cardioversion was attempted in 487 (51.6%), rate control was chosen in 31.4%, and 2 patients received a pacemaker (0.2%) because of sick sinus syndrome. Pharmacological cardioversion was performed in 276 of 487 (56.7%) patients; flecainide was the preferred drug in the majority of cases (93.1%). Electrical cardioversion was performed in 211 of 487 (43.3%) patients. Pharmacological cardioversion was successful in 80.1% of cases, ECV in 92.9%; the overall success rate of cardioversion was 85.8%. An overview of the treatment strategy is presented in Fig. 2.

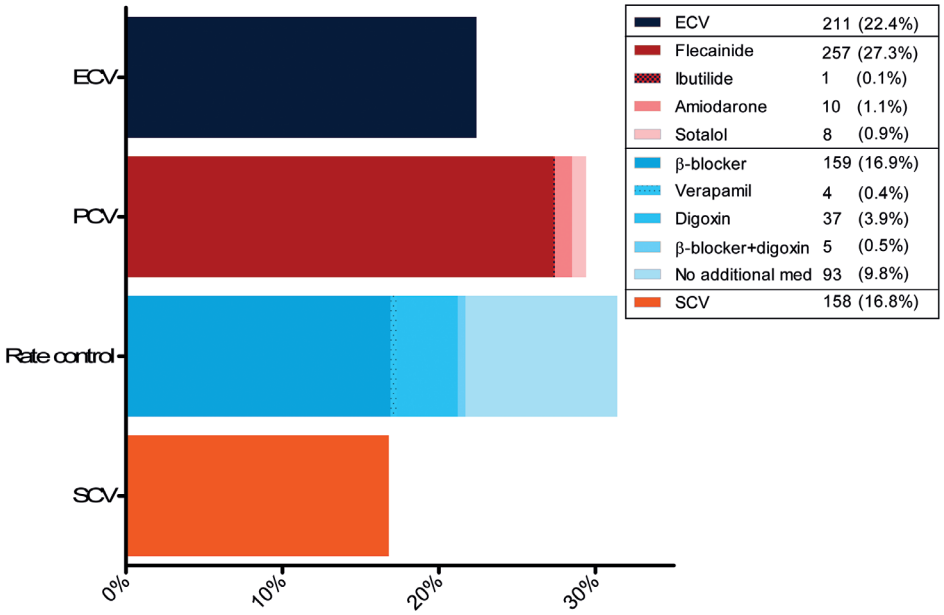

***Figure 2. Overall treatment strategy. ECV** electrical cardioversion, **PCV** pharmacological cardioversion, **SCV** spontaneous conversion.*

Spontaneous conversion

The median duration from onset of symptoms until the end of the observation period was 4.0 h (IQR 7, range 0-86 h) in patients with SCV, and 11.0 h (IQR 19, range 3-1355 h) in patients without SCV. The median observation time at the ED pending SCV was 32 min (IQR 81, range 0-165 min). The number of patients in SR after 1 h was 100 (10.6%), and after 2 h 138 (14.6%). The mean age of the SCV and non-SCV groups was comparable (70±11 vs 69±13 years, p=0.257, respectively). There was a trend towards more spontaneous cardioversions in female patients (53.8 vs 46.0%, p=0.073). Patients with SCV less frequently had a history of hypercholesterolaemia (25.9 vs 36.3%, p=0.013), coronary artery bypass grafting (1.9 vs 7.5%, p=0.009), chronic obstructive pulmonary disease (0.6 vs 3.8%, p=0.040), and less frequently had a history of valve surgery (1.3 vs 5.6%, p=0.021). Mean body mass index (BMI) was lower in patients with SCV (27.0 vs 28.5 kg/m^2, p=0.001). First-detected AF was more common in patients with SCV than in non-SCV patients (41.8 vs 32.0%, p=0.017, respectively). In addition, patients with SCV had a shorter median duration of symptoms (3.0 h; IQR 5 vs 8.0; IQR 19, p<0.001) and more often suffered symptoms of near-collapse (11.4 vs 6.1%, p=0.018), palpitations (81.6 vs 72.0%, p=0.012),

chest pain (27.8 vs 18.6%, p=0.008), and dizziness (20.3 vs 14.9%, p=0.093). Patients complaining of near-collapse more often had first-detected AF (58% vs 42%, p<0.001). Patients with SCV more often had a higher ventricular rate (125 vs 118 bpm, p=0.004), longer QTc time during AF (460 ms ±34 vs 452 ms ±34, p=0.035) and more often had a lower left atrial volume index (LAVI) (<42 ml/m^2) (61.3 vs 47.8%, p=0.004). A longer QTc was observed in patients who had a breakthrough arrhythmia [460±40 ms in patients with antiarrhythmic drugs (AAD) vs 450 ±40 ms in patients without AAD, p<0.001]).

Logistic regression analysis showed that duration of AF <24 h (OR 7.7, 95% CI 3.5-17.2, p<0.001), LAVI <42 ml/m^2 (OR 1.8, 95% CI 1.2-2.8, p=0.010), symptoms of near-collapse at presentation (OR 2.4, 95% CI 1.2-5.1, p=0.018), a lower BMI (OR 0.9, 95% CI 0.91-0.99, p=0.028), a longer QTc time during AF (OR 1.01, 95% CI 1.0-1.02, p=0.002) and first-detected AF (OR 2.5, 95% CI 1.6-3.9, p<0.001) were independent determinants of early SCV (Table 2).

In patients with a duration of AF <24 h, first-detected AF, and smaller LAVI, the SCV rate was high: 38% (38 of 99 patients).

Table 2. **Univariable and multivariable regression analyses for predictors of spontaneous conversion to sinus rhythm.**

	Univariable					**Multivariable**		
	Non-SCV, n=785		**SCV, n=158**		**p-value**	**OR**	**95% CI**	**p-value**
Demographics								
BMI	28.5	(±6.5)	27.0	(±4.6)	0.001	0.9	0.91-0.99	0.028
Presentation characteristics								
Duration <24 h	534	(68.0%)	143	(90.5%)	<0.001	7.7	3.5-17.2	<0.001
First-detected AF	251	(32.0%)	66	(41.8%)	0.017	2.5	1.6-3.9	<0.001
Near-collapse	48	(6.1%)	18	(11.4%)	0.018	2.4	1.2-5.1	0.018
Echo- and electrocardiography								
QTc (ms)	452	(±34)	460	(±34)	0.035	1.01	1.00-1.02	0.002
LAV index < 42 ml/m2	317	(47.8%)	84	(61.3%)	0.004	1.8	1.2-2.8	0.010

This model is based on n=759 due to missing data on left atrial volume index. ***AF*** *atrial fibrillation,* ***BMI*** *body mass index,* ***CI*** *confidence interval,* ***LA*** *left atrial, OR odds ratio,* ***SCV*** *spontaneous conversion*

DISCUSSION

The present study showed that early SCV to SR occurred in 16.8% of patients presenting with AF at the ED within a median time at the ED of 32 min. Duration of symptoms <24 h, first-detected AF, LAVI <42 ml/m^2, a lower BMI and symptoms of near-collapse or longer QTc time at presentation were independent determinants of early SCV.

Previous studies have reported variable SCV rates of acute AF ranging from 26 to 71%[1,5-11], mostly depending on differences in study design, observation period and patient selection criteria. Danias et al. included 356 in-hospital patients with symptomatic AF <72 h and observed a SCV rate of 68%. In the absence of initial AAD therapy, these investigators found that the best predictor of SCV was a duration of symptoms <24 h [1]. This was confirmed by Lindberg et al. [6], who reported a SCV rate of 54% in patients in hospital with first-onset AF (n=374). In 153 patients with paroxysmal AF and a symptom duration <24 h and without structural heart disease, heart failure or hyperthyroidism, Geleris and co-workers observed a SCV rate of 71.2%. In this homogeneous group, small

left atrial size was the only predictor for SCV[7]. Boriani et al. performed a randomised controlled trial of propafenone versus placebo for recent-onset AF (<7 days) and observed a SCV rate in the placebo group of 37% after 8 h of observation[11]. Sub-analyses of this study showed a higher likelihood of SCV in patients without underlying heart disease[11] and those aged <60 years[12].

The lower rate of SCV observed in our cohort is likely the result of shorter observation periods (censored at 3 h maximum) at the ED. The SCV rate we found is comparable to that in other reports of recent-onset AF by Vinson et al. (28.6%)[13] and Stiell et al. (26.5%)[10]. Vinson et al. investigated the management of recent-onset AF or atrial flutter at the ED. A total of 206 patients were included with a duration of symptoms <48 h. They found a SCV rate of 28.6%[13]. A similar SCV rate was reported by Stiell et al., who included 1068 patients with recent-onset AF (<48 h) at the ED. During a median observation period of 6.7 h, 26.5% of patients had SCV [10]. Sub-analyses of the ENSURE-AF trial, which included patients with non-valvular atrial fibrillation with a duration > 48 h and who were scheduled for ECV on anticoagulation therapy, have demonstrated SCV rates of 7.6%. In the sub-analysis of Cohen et al., a history of paroxysmal AF was the only predictor for SCV[14].

To the best of our knowledge, our study is the largest concerning determinants of early SCV and enables clinicians to identify patients who are most likely to convert spontaneously to SR. In our cohort, the following characteristics appeared to be determinants of early SCV at the ED: AF duration <24 h, first-detected AF, a lower LAVI, a lower BMI, a longer QTc time during AF and symptoms of near-collapse at presentation. These parameters are most likely indicative of early phases of AF evolution. A lower LAVI suggests that macroscopic electrical and structural remodelling of the atrium has not been evident yet or is at an early stage. It is well known that this is related to higher conversion rates[15,16]. Obesity is a well-known risk factor for developing AF[17] and a higher BMI is independently associated with progression from paroxysmal to permanent AF[18]; this could explain the higher SCV rate in patients with a lower BMI. Patients presenting with near-collapse during AF more often had first-detected AF, which may be related to the higher SCV rates seen in those patients.

'Wait-and-see approach' in acute AF

The substantial rates of SCV of acute AF in this and other reports[1,5-8,10], combined with the rising prevalence of AF, cost aspects and the possible complications associated with acute cardioversion may justify less aggressive arrhythmia management. A wait-and-see strategy for patients with stable AF with onset of symptoms <48 h encompasses standard rate control measures, adequate initiation of anticoagulation and delayed cardioversion within 48 h if necessary. In a small study investigating this wait-and-see approach, two-thirds of 35 patients had converted spontaneously within 48 h[5]. This finding was recently confirmed by the RACE 7 ACWAS trial, a multicentre randomised controlled trial which compared a wait-and-see approach (symptom alleviation and delayed cardioversion when necessary) with immediate cardioversion in patients with recent-onset AF[9,19]. This study showed that a wait-and-see approach is non-inferior with respect to the presence of SR at 4 weeks when compared to immediate cardioversion; almost 70% of the patients in the wait-and-see group had SCV to SR within 48 h. Those results support the opinion that a wait-and-see approach is a worthy alternative to discuss with patients but will not replace early cardioversion completely. Early cardioversion could be beneficial, since it shortens the time until conversion, which might eliminate symptoms earlier. However, in the above-mentioned study symptom control was similar in both groups[9]. Another advantage of early pharmacological conversion is the observation of the antiarrhythmic response, which tests the safety of a pill-in-the-pocket approach[20]. Therefore, patients with stable recent-onset AF and their physicians might choose between the two approaches in a shared decision-making process.

The results of the current study facilitate the identification of patients with a high likelihood of SCV to SR and the implementation of a wait-and-see approach. Identification of acute AF patients

susceptible to spontaneous restoration of SR may reduce the number of emergency visits (especially in stable patients with recurrent episodes and a known symptom-rhythm correlation), costs and unnecessary and potentially harmful treatment.

Limitations

Since this study was not designed to evaluate SCV rates, our results are probably an underestimation of the true SCV rate: patients who received active cardioversion might have converted spontaneously if a wait-and-see approach had been adopted. Due to the observational study design we could not adjust for this possible bias. Patients with pre-hospital SCV were included in the analysis. Even if the likelihood of those patients having AF was extremely high, one cannot be completely certain that those patients had an actual episode of AF, which could have led to an overestimation of the SCV rate.

CONCLUSION

Early SCV of acute AF occurs in almost one-sixth of admitted patients during a short initial observation in the ED. Spontaneous conversion is most likely to occur in patients with first-onset, short-duration AF episodes, lower BMI, and normal left atrial size.

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Arrhythm Electrophysiol Rev 2020;9:195-201.

Frequency and determinants of spontaneous conversion to sinus rhythm in patients presenting to the emergency department with recent-onset atrial fibrillation. A systematic review

ABSTRACT

The exact frequency as well as clinical determinants of spontaneous conversion (SCV) in patients with symptomatic recent-onset atrial fibrillation (AF) are unclear. The aim of this systematic review is to provide an overview on the frequency and determinants of SCV of AF in patients presenting at the emergency department (ED).

A comprehensive literature search was performed on SCV in patients presenting to the ED with AF. Twenty-five articles were included; twelve randomized controlled trials, thirteen observational studies. SCV rates range widely between 9 and 83%, also determinants of SCV varied between studies. The most important determinants of SCV include short duration of AF (<24 or <48 hours), low episode number, normal atrial dimensions, and absence of previous heart disease. The large variation in SCV rate and determinants of SCV was related to differences in duration of the observation period, in- and exclusion criteria and in variables used in the prediction models.

Keywords
Spontaneous conversion, atrial fibrillation, treatment, determinants of spontaneous conversion, systematic review

INTRODUCTION

In patients presenting at the emergency department (ED) with symptomatic recent-onset atrial fibrillation (AF), immediate restoration of sinus rhythm by pharmacological (PCV) or electrical cardioversion (ECV) is frequently performed[1,2]. Nevertheless, most of these patients convert spontaneously to sinus rhythm without the need of additional interventions[3-7]. Accordingly, several studies indicated that rate control to manage symptoms and wait for spontaneous conversion (SCV) is a reasonable alternative for the acute treatment of patients with recent-onset hemodynamically stable AF[8,9].

ECV is a relatively expensive procedure and, dependent on local routines, requires the involvement of nurses, an anesthesiologist and a cardiologist or emergency physician. Point-of-care identification of patients with recent-onset AF who will convert spontaneously after presentation, and therefore qualify for a wait-and-see approach would lower the number of required PCV and ECV procedures in the ED setting and reduce health care costs.

The exact frequency as well as clinical predictors of SCV to sinus rhythm in patients with symptomatic recent-onset AF are unclear. Appropriate selection of patients with a high likelihood of SCV is key to the wait-and-see approach. The present review focuses on the frequency and determinants of SCV of AF in patients presenting at the ED.

METHODS

Search methods and study selection

A literature search was performed to identify all English articles published that discussed SCV to SR in patients presenting to the ED with AF. Pubmed, Embase and Cochrane Library were searched for the keywords "spontaneous conversion", "SCV", "self-terminating ", "self terminating", "wait-and-see", "wait and see" AND "Atrial fibrillation", "AF", "AFib" AND "recent onset", "recent-onset", "acute", "paroxysmal", "first detected", "first-detected". References of included articles were reviewed to identify additional articles. All original articles were included if they discussed SCV to SR in patients presenting to the ED with AF. There were no exclusion criteria. The literature search and screening for eligibility were performed by two investigators independently (NAHAP, ANLH), disagreement was resolved by discussion until consensus was reached.

Outcome and data collection

The primary outcome was the SCV rate, secondary outcomes were determinants for SCV and adverse events. Data on study design, patient characteristics, intervention and treatment were extracted.

Quality assessment

All included articles were independently assessed for the risk of bias by the two reviewers using the Cochrane tool to assess the risk of bias for randomized controlled trials (RCT)[10] and the Risk of Bias in Non-randomized Studies- of Interventions (ROBINS-I) tool for the non-randomized studies[11]. The confounding domains considered relevant to the primary outcome a priori was consecutive patient inclusion. Disagreements between the reviewers were resolved by discussion.

Definitions

For the purpose of this review conversion was defined spontaneous if the patient converted to sinus rhythm without active cardioversion (either PCV or ECV), rate control and/or placebo medication were allowed. Accordingly, if patients were treated with placebo, digoxin, beta blockers or non-dihydropyridine calcium channel blockers and converted to sinus rhythm, it was considered

SCV for this review. The reported time until evaluation of the rhythm was used as observation time; if not reported, this was considered as no standardized observation time. Determinants of SCV were accumulated if the studies performed an analysis for determinants of SCV.

RESULTS

Screening and included studies

A comprehensive literature search identified 138 potentially relevant articles. After screening of title and abstract, exclusion of duplicates and critical review of full-text, 25 articles were included in this systematic review, **Figure 1**. Of the 25 included articles, twelve were randomized controlled trials, seven prospective observational cohort studies and six were retrospective observational cohort studies. An overview of abstracted data from included studies is provided in **Table 1**.

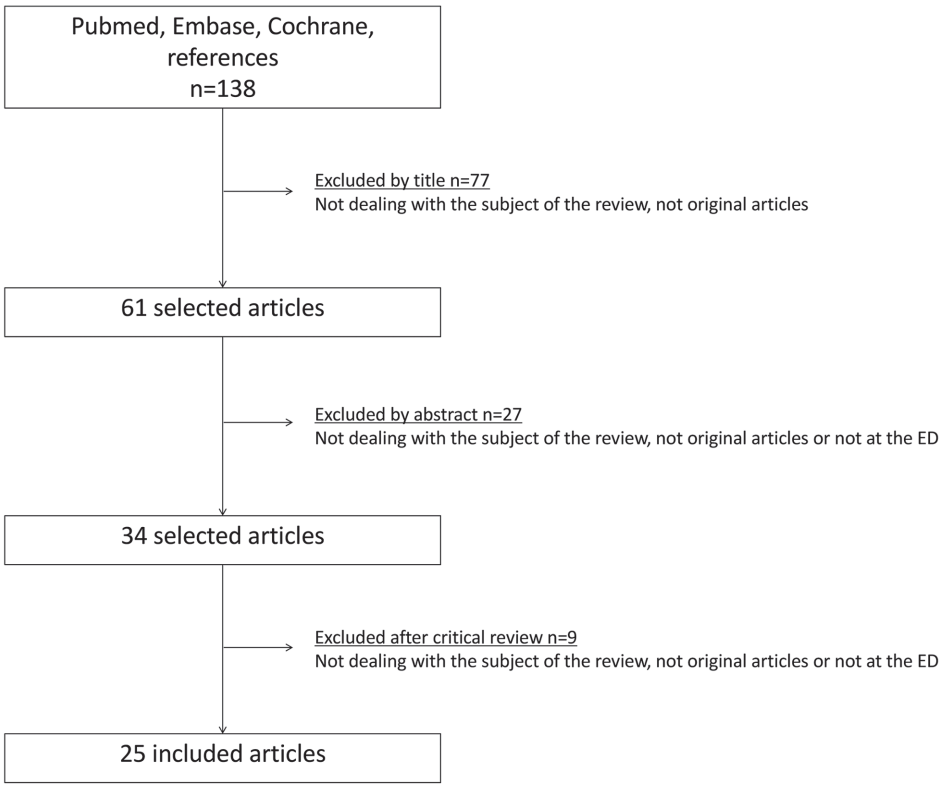

Figure 1. Flow chart of literature search.

Table 1. **Overview of abstracted data from included studies. More details are presented in the Supplementary file table S3.**

References, country	N centers/ N patients	Study design, intervention	Setting/ observation time	Included	SCV rate n(%)
RCT					
Falk et.al.[25] 1987 U.S.	1/36	RCT, oral digoxin vs. placebo	ED/ hospitalized, 18 h observation	new-onset AF seen in the ED or on the wards (duration <7 days)	17/36 (47.2%)
Capucci et.al.[18] 1992 Italy	1/62	RCT, oral flecainide vs. iv amiodaron vs. placebo	ED/ hospitalized, 8h observation	recent-onset AF (<7days)	10/21 (48%)
Capucci et.al.[16] 1994 Italy	1/181	RCT, oral propafenone vs. oral flecainide vs. placebo	ED/ hospitalized, 8h observation	recent-onset AF (<7days) (if AF> 72 h only if chronically anticoagulated)	24/62 (39%)
Bellandi et.al.[21] 1996 Italy	1/182	RCT, iv propafenone vs. placebo	ED/ hospitalized, 24h observation	paroxysmal AF lasting >30 minutes but <7 days	27/84 (32%)
Galve et.al.[22] 1996 Spain	1/100	RCT, iv amiodaron vs. placebo	ED/ hospitalized, 24h observation	recent-onset AF (<7days)	30/50 (60%)
DAAF trial group[19] 1997 Sweden	13/239	RCT, iv digoxin vs. iv placebo	ED/ hospitalized, 16h observation	recent-onset AF (<7days)	116/239 (48.5%)
Azpitarte et.al.[23] 1997 Spain	1/55	RCT, oral propafenone vs. placebo	ED/ hospitalized, 24h observation	all patients with acute AF presenting at the ED	19/26 (73%)
Boriani et.al.[17] 1997 Italy	3/240	RCT, oral propafenone vs. placebo	ED/ hospitalized, 8h observation	recent-onset AF (< 7 days) (if AF> 72 h only if chronically anticoagulated)	45/121(37.2%)
Cotter et.al.[7] 1999 Israel	1/100	RCT, iv amiodaron vs. placebo	ED/ hospitalized, 24h observation	paroxysmal atrial fibrillation <48 h and if they had had at least one previous episode of paroxysmal atrial fibrillation	32/50 (64%)
Hohnloser et.al.[15] 2004 Germany	34/201	RCT, iv tedisamil vs. placebo	ED/ hospitalized, 2.5h observation	symptomatic AF or AFL of 3- to 48-h duration, BP >90 mmHg systolic and BP <105 mmHg diastolic.	4/46 (8.7%)
Hassan et.al.[24] 2007 U.S.	2/50	RCT iv diltiazem vs. iv esmolol	ED/ 24h observation (time after drug infusion)	new-onset or paroxysmal AF and a rapid ventricular rate (>100 beats per minute over 10 minutes)	20/50 (40%)

Table 1. (continued)

References, country	N centers/ N patients	Study design, intervention	Setting/ observation time	Included	SCV rate n(%)
Pluymaekers et.al.[9] 2019 Netherlands	15/437	RCT, early cardioversion vs. wait-and-see	ED/ 48h observation	hemodynamic stable, symptomatic patients with AF <36hours	150/218 (69%)
Non RCT					
Danias et.al.[3] 1998 U.S.	2/356	Prospective	ED/ hospitalized, observation 4.6 days (time to CV 1.7 days)	AF <72h	242/356 (68%)
Dell'Orfano et.al.[26] 1999 U.S.	1/114	Retrospective	ED/ <48h observation	primary diagnosis of AF (ICD9 code 427.31), documentation of the arrhythmia by single-channel or 12-lead ECG	57/114 (50%)
Mattioli et.al.[29] 2000 Italy	1/140	Prospective	ED/hospitalized, 48h observation	lone AF with a clinically estimated duration of <6 hours	108/140 (77.1%)
Mattioli et.al.[28] 2005 Italy	1/116	Prospective, case control	ED/ 48h after onset of symptoms	hemodynamically stable patients, hospitalized for an acute episode of lone AF (<6h onset of symptoms)	72/116 (62.1%)
Geleris et.al.[6] 2001 Greece	1/153	Prospective	ED/ 24h observation	consecutive patients with recent onset AF (< 24h)	109/153 (71.2%)
Dixon et.al.[27] 2005 U.S.	1/135	Retrospective,	ED/ hospitalized, in general monitoring up to 48h	a primary diagnosis of AF (essential reason for hospital admission)	71/135 (52.6%)
Doyle et.al.[8] 2011 Australia	1/35	Prospective, wait-and-see	ED/ 48h wait-and-see	patients with stable acute AF <48h	22/35 (62.9%)
Perrea et.al.[13] 2011 Greece	1/141	Retrospective pilot study: SCV, amiodaron	ED/ no observation time	AF at the time of presentation (<48h)	28/141 (19.6%)
Scheuermeyer et.al.[12] 2012 Canada	2/927	Retrospective	ED/ no observation time	consecutive patients with AF	121/927 (13.1%)
Lindberg et.al.[5] 2012 Denmark	1/374	Retrospective	ED/ <48h observation	consecutive patients admitted to hospital with first onset AF	203/374 (54%)

Table 1. (continued)

References, country	N centers/ N patients	Study design, intervention	Setting/ observation time	Included	SCV rate n(%)
Vinson et.al.[14] 2012 U.S.	3/206	Prospective	ED/ no observation, small subgroup 48 wait and see	recent-onset AF (<48 h)	59/206 (28.6%) 11/15 (68.8%) WAS
Choudhary et.al. [20]2013 Sweden	1/148	Retrospective	ED/ SCV <18h after symptom onset	patients with paroxysmal AF<48h	48/148 (32.4%)
Abadie et.al.[30] 2019 U.S.	1/157	Prospective	ED/ 30-90 days observation	low-to-moderate risk AF patient	48h 98/157 (63%), 30 d 113/136 (83%)

AF denotes atrial fibrillation, AFL denotes atrial flutter, ED denotes emergency department, h denotes hours, iv denotes intravenous, RCT denotes randomized controlled trial, SCV denotes spontaneous conversion.

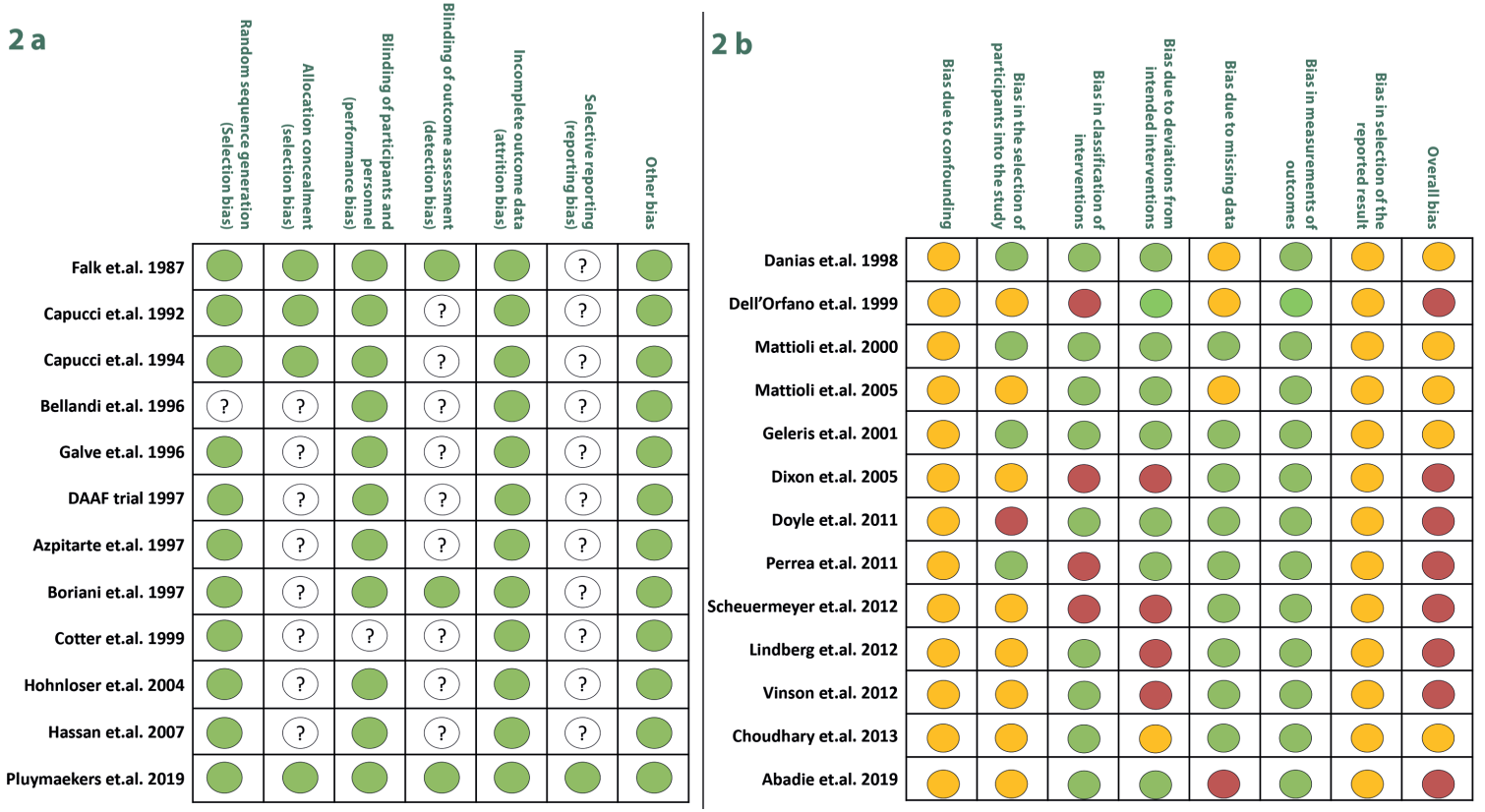

Figure 2. *Risk of bias assessment.* ***Panel 2a.*** *Overview of risk of bias assessment for the randomized controlled trials. Green circle represents a low risk of bias and for white circles with question mark the risk of bias could not be established.* ***Panel 2b.*** *Overview of risk of bias assessment for the observational studies. Green circle represents a low risk of bias, orange circle an intermediate risk of bias, red circle a high risk of bias.*

Quality assessment

Four of the twelve included randomized controlled trials were multicenter clinical trials, nine trials compared acute cardioversion versus placebo/rate control, two trials compared rate control versus placebo and one trial compared two different rate control strategies. A complete overview of assessment of risk of bias for the RCTs are reported in **Figure 2a** and **Supplementary file S1.**

An overview of the risk of bias assessment for the observational studies is reported in **Figure 2b** and **Supplementary file S2**. Eight studies were assessed to have a serious risk of bias and five a moderate risk of bias.

Spontaneous conversion without a standard observation period (early spontaneous conversion)

Early spontaneous conversion was described in four studies[12-15], and conversion rates ranged from 8.7%-28.6% (**Figure 3**). Mean age was 64 years, 41% were female. Main difference between those studies was the duration of onset of symptoms. Perrea et al., Vinson et al. and Hohnloser et al. included only patients with onset of symptoms <48 hours[13-15]. On the contrary, Scheuermeyer et al. included all patients with AF irrespective of the time of symptom onset[12]. An overview of in- and exclusion criteria is shown in the **Supplementary file S3**.

Spontaneous conversion after a standard observation period

Three trials reported a spontaneous conversion rate at eight hours ranging from 37-48%. Two were randomized controlled trials which compared oral propafenone versus placebo[16,17] and one trial compared oral flecainide to intravenous amiodarone and placebo[18]. Those trials were comparable concerning the in- and exclusion criteria and patient characteristics (age 58[18] vs. 58.5[17] vs. 60[16] years, respectively; mean AF duration 28 hours, 30.5 hours and 35 hours, respectively).

A longer observation period, up to 24 hours, was described by nine trials and spontaneous conversion rates varied in those trials from 32-73%[6,7,19-25]. Seven studies were randomized controlled trials and two were observational. Baseline characteristics were similar among all these studies, with mean age 64 years

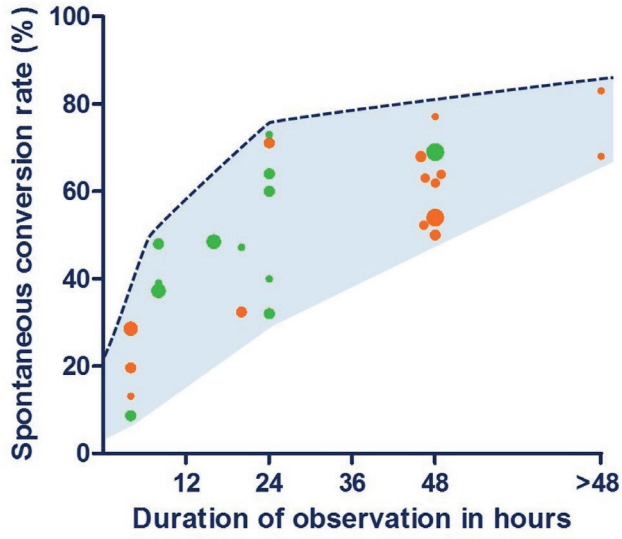

Figure 3. Spontaneous conversion rate for different periods of observation times. *In green randomized controlled trials, in orange observational studies. The diameter of the circle represents the size of the population included in the trial.*

and on average 47% of patients being female. Notably, inclusion criteria differed with respect to the duration of onset of symptoms at presentation, ranging from less than 24 hours up to 7 days.

A higher spontaneous conversion rate (52-77%) was reported in the studies with a long observation period up to 48 hours (mean age 63 years, 38% female)[5,8,9,14,26-29]. In two observational studies the observation period extended even beyond 48 hours. Danias et al.[3] reported a spontaneous conversion rate of 68% after a median observation time of 4.6 days. Abadie et al.[30] reported a spontaneous conversion rate of 63% at 48 hours and up to 83% after 30 days (**Figure 3**).

Determinants of spontaneous conversion

Determinants of SCV varied among studies (**Table 2)**. Only one study reported on determinants of early SCV, therefore no comparison was made between early and late SCV determinants. Perrea et.al. reported a formula ([heart rate/systolic blood pressure] + 0.1 x number of past AF episodes) to determine the likelihood of SCV[13]. Using this formula, a cutoff value of 1.3 was found to have a sensitivity of 78.6% and specificity of 77.9% for predicting SCV. Duration of the AF episode at presentation at the ED appeared an important determinant for SCV in three studies. Dell'Orfano et al. and Lindberg et al. reported both a higher likelihood of SCV in patients with a duration of AF <48 hours. Danias et al. reported a higher SCV rate in patients with a duration of AF <24 hours. Apart from episode duration, also first episode of AF, absent previous supraventricular arrhythmias and normal left atrial dimensions were found important determinants of SCV[6,7,20,22]. Patients without heart failure or underlying heart disease had as well a higher SCV rate[7,17,22]. Remarkably, Choudhary et al.[20] reported a higher SCV rate in patients with ischemic heart disease. In this study also a lower atrial fibrillatory rate was associated with a higher SCV rate. Mattioli et al. compared personality, socio-economic factors and acute stress of patients with SCV to a matched control group. Patients with acute stress or a type A behavior pattern had the highest probability of SCV; coffee consumption and a high body mass index reduced the SCV rate. Of note, multivariate analyses to determine independent determinants of SCV were not performed in every study and the strategy to include variables in the prediction models varied between studies.

Adverse events and thromboembolic complications

Adverse events were mainly reported in the RCTs,[7,9,15-19,21-24] and in only two observational studies.[8,14] An overview of reported adverse events is provided in **Table S3 of the Supplementary file** (thromboembolic and bleeding complications are reported below). Overall adverse events were higher in the cardioversion group compared to the rate control/placebo groups (**Table S4 of the Supplementary file**). Reported adverse events in the rate control and placebo group were sustained atrial flutter/ tachycardia, pauses >2sec and/or bradycardia, vomiting, hypotension and in one case heart failure. In the Digitalis in Acute AF (DAAF) trial, one patient in the digoxin group experienced circulatory distress due to previously undiagnosed hypertrophic obstructive cardiomyopathy[19]. Hohnloser et al. reported in 2% of cases in the placebo group ventricular tachycardia, no further details were provided[15]. Cotter et al. reported a small non-Q wave myocardial infarction 24 hours after admission in one patient[7]. Only six studies (2 RCT, 4 observational) reported on thromboembolic or bleeding complications, which occurred rarely. Lindberg et al. and Doyle et al. did not observe thromboembolic complications[5,8]. Cotter et al. reported one transient ischemic attack 10 hours after admission while the patient was in AF[7]. Stroke risk scores (i.e. CHA_2DS_2-VASc[31] or $CHADS_2$[32]) were not yet available at the time of this trial and therefore not known for this patient. Scheuermeyer et al. reported two strokes within 30 days, a 59 year old man on rate control medication and known with a history of diabetes, hypertension and treated with warfarin presented at day 27 with a stroke due to bleeding (INR at that time 4.1)[12]. And an 82 year old man, in whom no specific AF treatment was performed, suffered a stroke 24 days after the ED visit. Due to a high perceived bleeding risk this patient was not on anticoagulant treatment. Vinson et al. reported two strokes within 48 hours after the ED

visit, both patients were not on anticoagulation therapy. In one patient anticoagulation was withheld after successful ECV because of prior hemorrhagic complications, and one stroke patient underwent rate control during the ED visit but refused anticoagulation treatment[14]. In the RACE 7 ACWAS trial[9] two patients had cerebral embolism. One occurred five days after SCV while on anticoagulation treatment since the previous ED visit, the other stroke occurred ten days after electrical cardioversion, also in this patient anticoagulation treatment was initiated during the ED visit.

Table 2. **Determinants of spontaneous conversion.**

References, country	Determinants of SCV
Falk et.al.[25] 1987, U.S.	NA
Capucci et.al.[18] 1992, Italy	NA
Capucci et.al.[16] 1994, Italy	NA
Bellandi et.al.[21] 1996, Italy	NA
Galve et.al.[22] 1996, Spain	Absence of congestive heart failure and history of SVT, smaller left atrial size
DAAF trial group[19] 1997, Sweden	NA
Azpitarte et.al.[23] 1997, Spain	NA
Boriani et.al.[17] 1997, Italy	Patients without heart disease (defined as the absence of cardiac abnormalities other than AF)
Cotter et.al.[7] 1999, Israel	(Univariable) left atrial size <45 mm, EF > 45% and no significant mitral regurgitation
Hohnloser et.al.[15] 2004, Germany	NA
Hassan et.al.[24] 2007, U.S.	NA
Pluymaekers et.al.[9] 2019, Netherlands	NA
Non-RCT	
Danias et.al.[3] 1998, U.S.	Duration of AF <24h
Dell'Orfano et.al.[26] 1999, U.S.	Duration of AF <48h
Mattioli et.al.[29] 2000, Italy	Onset AF during sleep, elevated ANP
Mattioli et.al.[28] 2005, Italy	Patients with acute stress showed the highest probability of spontaneous conversion followed by patients with Type A behavior
Geleris et.al.[6] 2001, Greece	Left atrial dimension (univariable)
Dixon et.al.[27] 2005, U.S.	NA
Doyle et.al.[8] 2011, Australia	NA
Perrea et.al.[13] 2011, Greece	([HR/systolic blood pressure] + 0.1 x number of past AF episodes)
Scheuermeyer et.al.[12] 2012, Canada	NA
Lindberg et.al.[5] 2012, Denmark	Duration of AF <48h
Vinson et.al.[14] 2012, U.S.	NA
Choudhary et.al.[20] 2013, Sweden	AFR < 350 fpm, presence of IHD, and first-ever episode of AF
Abadie et.al.[30] 2019, U.S.	NA

AF *denotes atrial fibrillation,* ***AFR*** *atrial fibrillatory rate,* ***ANP*** *atrial natriuretic peptide,* ***EF*** *ejection fraction,* ***HR*** *heart rate, h hour,* ***IHD*** *ischemic heart disease,* ***NA*** *not available,* ***SVT*** *supraventricular tachycardia (previous atrial arrhythmias). Boriani et.al. reported in the same population divided by age, patients with age <60years as predictor for SCV[35].*

DISCUSSION

This systematic review provides an overview of the frequency and determinants of SCV of AF in patients presenting at the ED. SCV rates range widely between 9 and 83% depending on the duration of the observation period, and differences in the in- and exclusion criteria (e.g. including first-detected versus all-comers, or excluding patients on antiarrhythmic drugs or digoxin, or not). Also predictors of spontaneous conversion varied between studies. The most important determinants of SCV include short duration of AF (<24 or <48 hours versus longer duration at ED presentation, although that was not supported by all studies)[3,5,26], low episode number (first-detected AF versus recurrent AF or previous supraventricular arrhythmias), normal atrial dimensions, and absence of previous heart failure or other underlying heart diseases. Notably, variation between studies concerning predicting factors also may relate to relatively small patient numbers per study and different strategies when including specific variables in the prediction models.

Many patients presenting at the ED with recent-onset AF may convert spontaneously if a sufficiently long observation period is used. The majority of SCVs occurs within the first 24-48 hours of observation in patients with relatively short duration of symptoms at the time of presentation. Presumably this finding relates to the intrinsic patient-specific pattern of self-terminating symptomatic AF in patients reporting to the ED, i.e. long enough to cause symptoms and to be still present at the ED, yet self-terminating. This pattern of AF was recently reported as the 'legato' (rather than 'staccato') type of paroxysmal AF[33] which in the majority of patients lasts hours. Patients with a long 'legato' pattern of a day to a few days of AF are a minority and responsible for non-conversions seen in the setting of the ED[3,5,26]. From the current data we cannot tell whether patients with "early" SCV have a different risk factor profile or different mechanism of termination compared to patients with "late" SCV [33]. More studies with continuous or intense longitudinal rhythm monitoring are needed to investigate whether those subtypes of recent-onset AF indeed exist and differ in pathophysiology, underlying risk factors, mechanism of termination or even prognosis.

The duration until SCV was assessed variably, some studies taking the symptom onset into account whereas others started measuring from the beginning of the observation period (often from presentation at the ED), all until the time-point of documented SR. This may have contributed to the observed variance in SCV rates. For instance, Mattioli et al. reported a SCV rate of 77% within 48 hours and included only patients with first-onset AF and a symptom onset <6 hours. This stringent selection of patients could explain the higher conversion rate compared to the 52.6% reported by Dixon et al. and 54% reported by Lindberg et al. The latter studies included patients with first-onset AF *regardless* the duration of AF with the inherent chance to also include a significant subset of patients with longer lasting episodes, in turn responsible for non-conversion even after long observation times up till 48 hours. Whether a more exact documentation of the actual AF duration (e.g. by continuous rhythm monitoring or using the onset of symptoms as a surrogate of AF-onset) would reveal a more detailed classification of the AF subtype and whether this will explain the variance in SCV rates warrants further study.

No study provided data on patient-reported self-termination or on a previously recognized pattern of SCV in those who had experienced SCVs of symptomatic AF in the past. Many patients with recent-onset AF have likely experienced previous self-termination and will experience self-termination in the future. Knowing that the pattern may be quite constant, such information could quite robustly guide the choice between early cardioversion and a wait-and-see approach.

The majority of the included studies evaluated SCV during a hospitalized observation period and did not report safety concerns. Only three studies evaluated a wait-and-see approach which included sending patients home while still in AF[8,9,30]. Although those studies were not powered to assess safety, complications were infrequent and similar when compared to active cardioversion[9]. Regardless the choice of rate or rhythm control for the acute management, early diagnostics and

treatment of cardiovascular and non-cardiovascular risk factors is an important component of AF management and can help to maintain sinus rhythm and to reduce AF burden. A wait-and-see approach may enhance systematic identification of risk factors and concomitant conditions, since it shifts the focus away from acute rhythm control strategies.

A better refinement of determinants of SCV and a categorical classification of patients in different subtypes of recent-onset AF will be crucial to allow a personalized guidance of a wait-and-see approach, which may be a good alternative to acute cardioversion in the management of recent-onset AF. Obviously, non-self-terminating AF patients do not qualify for a wait-and-see approach, especially also because a recent study suggested less arrhythmia recurrences and a reduction in atrial size with early cardioversion in persistent AF patients[34]. During a short term follow up (4 weeks) in patients with recent-onset AF, no difference was seen between early cardioversion and a wait-and-see approach in terms of recurrent episodes of AF, time to first recurrence and quality of life. No data is available on the long term effects and the progression of atrial substrate.

CONCLUSION

There is a large variation in SCV rate, duration till SCV, and determinants of SCV reported in the literature mainly due to differences in duration of the observation period, differences in the in- and exclusion criteria and different variables used in the prediction models. Future studies are needed to investigate the optimal waiting period in a wait-and-see approach, to define different subtypes of recent-onset AF and to assess the long-term consequences of a wait-and-see approach on the progression of atrial remodeling.

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SUPPLEMENTARY FILE

Frequency and determinants of spontaneous conversion to sinus rhythm in patients presenting to the emergency department with recent-onset atrial fibrillation. A systematic review.

SUPPLEMENTARY CONTENTS

Table S1. **overview of risk of bias assessment for the Randomised Controlled Trials.**

	Falk et.al.[1] 1987	Capucci et.al.[2] 1992	Capucci et.al.[3] 1994	Bellandi et.al.[4] 1996	Galve et.al.[5] 1996	DAAF trial[6] 1997
Selection bias	**Low risk/ Unclear**	**Low risk/ Unclear**	**Low risk/ Unclear**	**Low risk/ Unclear**	**Low risk/ Unclear**	**Low risk/ Unclear**
Random sequence generation	Patients were randomly assigned	Patients were randomly assigned	Patients were randomly assigned	Patients were randomly assigned	Patients were randomly assigned	Patients were randomly assigned
Allocation concealment	Method of concealment is not described	Method of concealment is not described	Method of concealment is not described	Method of concealment is not described	Method of concealment is not described	Method of concealment is not described
Perfor-mance bias	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Blinding of participants and personnel	Participants nor investigators were aware of the capsule content	Single blinded, patients were not aware of treatment	Single blinded, patients were not aware of treatment	Single blinded, but the outcome is not likely to be influenced by lack of blinding	Single blinded, patients were not aware of treatment	Double-blinded trial
Detection bias	**Low risk**	**Unclear**	**Unclear**	**Unclear**	**Unclear**	**Unclear**
Blinding of outcome assessment	Evaluation of endpoint (ECG) was performed before unblinding	Insufficient information	Insufficient information	Insufficient information	Insufficient information	Insufficient information
Attrition bias.	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Incomplete outcome data	No missing data concerning primary outcome	No missing data concerning primary outcome	No missing data concerning primary outcome	No missing data concerning primary outcome	No missing data concerning primary outcome	No missing data concerning primary outcome
Reporting bias.	**Unclear risk**	**Unclear risk**	**Unclear risk**	**Unclear risk**	**Unclear risk**	**Unclear risk**
Selective reporting	Insufficient information (no protocol available)	Insufficient information (no protocol available)	Insufficient information (no protocol available)	Insufficient information (no protocol available)	Insufficient information (no protocol available)	Insufficient information (no protocol available)
Other bias.	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Other sources of bias	No	No	No	No	No	No

	Azpitarte et.al.[7] 1997	Boriani et.al.[8] 1997	Cotter et.al.[9] 1999	Hohnloser et.al.[10] 2004	Hassan et.al.[11] 2007	Pluymaekers et.al.[12] 2019
	Low risk/ Unclear	**Low risk/ Unclear**	**Low risk/ Unclear**	**Low risk/ Unclear**	**Low risk/ Unclear**	**Low risk/ Low risk**
	Patients were randomly assigned	Patients were randomly assigned	Patients were randomly assigned	Patients were randomly assigned	Patients were randomly assigned	Patients were randomly assigned
	Method of concealment is not described	Method of concealment is not described	Method of concealment is not described	Method of concealment is not described	Method of concealment is not described	Web-based randomization
	Low risk	**Low risk**	**Unclear**	**Low risk**	**Low risk**	**Low risk**
	Double-blinded trial	Single blinded,- patients were not aware of treatment	Insufficient information	Double-blinded trial	No blinding, but the outcome is not likely to be influenced by lack of blinding	No blinding, but the outcome is not likely to be influenced by lack of blinding
	Unclear	**Low risk**	**Unclear**	**Unclear**	**Unclear**	**Low risk**
	Insufficient information	Blinded endpoint evaluation	Insufficient information	Insufficient information	Insufficient information	Blinded endpoint evaluation
	Low risk	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
	No missing data concerning primary outcome	No missing data concerning primary outcome	No missing data concerning primary outcome	No missing data concerning primary outcome	No missing data concerning primary outcome	Missing outcome data balanced between groups, sensitivity analysis is performed to adjust for this possible bias
	Unclear risk	**Unclear risk**	**Unclear risk**	**Unclear risk**	**Unclear risk**	**Low risk**
	Insufficient information (no protocol available)	Insufficient information (no protocol available)	Insufficient information (no protocol available)	Insufficient information (no protocol available)	Insufficient information (no protocol available)	Protocol and SAP available all relevant pre-specified outcomes have been reported
	Low risk	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
	No	No	No	No	No	No

Table S2. **overview of risk of bias assessment for observational studies.**

Domain of bias	Danias et.al.[13] 1998	Dell'Orfano et.al.[14] 1999	Mattioli et.al.[15] 2000	Mattioli et.al.[16] 2005	Geleris et.al.[17] 2001	Dixon et.al.[18] 2005
Bias due to confounding	Moderate risk: due to the study designs all other studies were expected to have confounding (even if adequately adjusted)	Moderate risk: due to the study designs all other studies were expected to have confounding (even if adequately adjusted)	Moderate risk: due to the study designs all other studies were expected to have confounding (even if adequately adjusted)	Moderate risk: due to the study designs all other studies were expected to have confounding (even if adequately adjusted)	Moderate risk: due to the study designs all other studies were expected to have confounding (even if adequately adjusted)	Moderate risk: due to the study designs all other studies were expected to have confounding (even if adequately adjusted)
Bias in the selection of participants into the study	Low risk included consecutive patients who fulfill in/ exclusion criteria	Moderate risk Authors did not report consecutive inclusion. AF diagnosis was based on ICD9 code, this can be an underes-timation.	Low risk included consecutive patients who fulfill in/ exclusion criteria	Moderate risk Authors did not report consecutive inclusion	Low risk included consecutive patients who fulfill in/ exclusion criteria	Moderate risk Authors report consecutive inclusion. AF diagnosis was based on ICD9 code, this can be an underestimation.
Bias in classification of interven-tions	Low risk Groups well defined	Serious risk Intervention group not well defined. Not clear if treatment plan was previous defined.	Low risk Groups well defined	Low risk Groups well defined	Low risk Groups well defined	Serious risk Treatment strategy was up to the attending physician. In patients in whom a PCV or ECV is performed SCV could have occurred if a longer observation period was allowed.
Bias due to deviations from intended interven-tions	Low risk No deviations from indented intervention due to study design	Low risk In patients without SCV, PCV or ECV was performed, this is considered normal for clinical practice	Low risk In patients without spontaneous conversion a PCV or ECV was performed 48h	Low risk In patients without SCV an ECV was performed, this is considered normal for clinical practice	Low risk No deviations from intended intervention described	Serious risk deviations from the intended intervention are likely to impact the outcome (early PCV or ECV could influence SCV rate)

Table S2. (continued)

Domain of bias	Danias et.al.[13] 1998	Dell'Orfano et.al.[14] 1999	Mattioli et.al.[15] 2000	Mattioli et.al.[16] 2005	Geleris et.al.[17] 2001	Dixon et.al.[18] 2005
Bias due to missing data	Moderate risk The authors report missing data on echocardiographic parameters. Not clear whether this is equal divide over the two groups	Moderate risk The authors report missing data on duration of symptoms. This was equal divide over the two groups	Low risk: data reasonably complete, no missing reported	Moderate risk: The authors do not report missing data, for primary analysis data seems complete however, of only 109/116pts follow up is available	Low risk: data reasonably complete, no missing reported	Low risk The authors report missing data on three patients regarding there rhythm, data reasonably complete.
Bias in measure-ments of outcomes	Low risk The outcome measurement seems objective and comparable between groups	Low risk The outcome measurement seems objective and comparable between groups	Low risk The outcome measurement seems objective and comparable between groups	Low risk The outcome measurement seems objective and comparable between groups	Low risk The outcome measurement seems objective and comparable between groups	Low risk The outcome measurement seems objective and comparable between groups
Bias in selection of the reported result	Moderate risk No previous analysis plan available. Reported results are in line with description in methods.	Moderate risk No previous analysis plan available. Reported results are in line with description in methods.	Moderate risk No previous analysis plan available. Reported results are in line with description in methods.	Moderate risk No previous analysis plan available. Reported results are in line with description in methods	Moderate risk No previous analysis plan available. Reported results are in line with description in methods	Moderate risk No previous analysis plan available. Reported results are in line with description in methods
Overall bias	**Moderate risk of bias**	**Serious risk of bias**	**Moderate risk of bias**	**Moderate risk of bias**	**Moderate risk of bias**	**Moderate risk of bias**

Table S2. (continued)

Domain of bias	Doyle et.al.[19] 2011	Perrea et.al.[20] 2011	Scheuermeyer et.al.[21] 2012	Lindberg et.al.[22] 2012	Vinson et.al.[23] 2012	Choudhary et.al.[24] 2013	Abadie et.al.[25] 2019
Bias due to confounding	Moderate risk: due to the study designs all other studies were expected to have confounding (even if adequately adjusted)	Moderate risk: due to the study designs all other studies were expected to have confounding (even if adequately adjusted)	Moderate risk: due to the study designs all other studies were expected to have confounding (even if adequately adjusted)	Moderate risk: due to the study designs all other studies were expected to have confounding (even if adequately adjusted)	Moderate risk: due to the study designs all other studies were expected to have confounding (even if adequately adjusted)	Moderate risk: due to the study designs all other studies were expected to have confounding (even if adequately adjusted)	Moderate risk: due to the study designs all other studies were expected to have confounding (even if adequately adjusted)
Bias in the selection of participants into the study	Serious risk: Patients were incl uded at the discretion of the treating doctor if they were considered to have stable acute AF and suitable for a rhythm control strategy.	Low risk included consecutive patients who fulfill in/exclusion criteria	Moderate risk included consecutive patients who fulfill in/exclusion criteria. AF diagnosis was based on ICD10 code, this can be an underestimation.	Moderate risk Authors did not report consecutive inclusion.	Moderate risk Authors did not report consecutive inclusion.	Moderate risk the authors do not report consecutive inclusion, AF diagnosis was based on ICD10 code, this can be an underes-timation.	Moderate risk the authors do not report consecutive inclusion.
Bias in classification of interven-tions	Low risk Groups well defined	Serious risk intervention group not well defined, unclear how long observation was to observe SCV and when iv. loading dose amiodaron was start. This could influence outcome	Serious risk Treatment strategy was up to the attending physician. In patients who a PCV or ECV is performed SCV could have occurred if a longer observation period was allowed	Low risk Groups well defined	Low risk Groups well defined	Low risk Groups well defined	Low risk Groups well defined
Bias due to deviations from intended interventions	Low risk In patients without SCV, an ECV was performed, this is considered normal for clinical practice	Low risk In patients without SCV, loading dose amiodarone was started and if not successful amiodaron was administrated for 24h. No deviations reported.	Serious risk deviations from the intended intervention are likely to impact the outcome (early PCV or ECV could influence SCV rate)	Serious risk Treatment strategy was up to the attending physician. In patients who a PCV or ECV is performed SCV could have occurred if a longer observation period was allowed	Serious risk Treatment strategy was up to the attending physician. In patients who a PCV or ECV is performed SCV could have occurred if a longer observation period was allowed	Moderate risk In 43 patients an ECV was performed within 18hours, SCV could have occurred if a longer observation period was allowed. Those patients were excluded for the assessment of SCV rate	Low risk In patients without SCV, after 30 days an ECV was performed if the cardiologist felt this was appropriate.

Table S2. (continued)

Domain of bias	Doyle et.al.[19] 2011	Perrea et.al.[20] 2011	Scheuermeyer et.al.[21] 2012	Lindberg et.al.[22] 2012	Vinson et.al.[23] 2012	Choudhary et.al.[24] 2013	Abadie et.al.[25] 2019
Bias due to missing data	Low risk: data reasonably complete, no missing reported	Low risk: data reasonably complete, no missing reported	Low risk Data reasonably complete, the authors report missing data on echocardiography. However, echocardiography was not a study endpoint/ evaluation	Low risk: data reasonably complete, no missing reported	Low risk Data reasonably complete, the authors report missing however this is not likely to affect the outcome	Low risk: data reasonably complete, no missing reported	Serious risk: The authors report missing data on primary endpoint (rhythm at FU: the transition clinic and after 30 days). This is likely to affect the outcome
Bias in measurements of outcomes	Low risk The outcome measurement seems objective and comparable between groups	Low risk The outcome measurement seems objective and comparable between groups	Low risk The outcome measurement seems objective and comparable between groups	Low risk The outcome measurement seems objective and comparable between groups	Low risk The outcome measurement seems objective and comparable between groups	Low risk The outcome measurement seems objective and comparable between groups	Low risk The outcome measurement seems objective and comparable between groups
Bias in selection of the reported result	Moderate risk No previous analysis plan available. Reported results are in line with description in methods	Moderate risk No previous analysis plan available. Reported results are in line with description in methods	Moderate risk No previous analysis plan available. Reported results are in line with description in methods	Moderate risk No previous analysis plan available. Reported results are in line with description in methods	Moderate risk No previous analysis plan available. Reported results are in line with description in methods	Moderate risk No previous analysis plan available. Reported results are in line with description in methods	Moderate risk No previous analysis plan available. Reported results are in line with description in methods
Overall bias	**Serious risk of bias**	**Serious risk of bias**	**Serious risk of bias**	**Serious risk of bias**	**Serious risk of bias**	**Moderate risk of bias**	**Serious risk of bias**

Table S3. **Extended overview in- and exclusion criteria, adverse events and thromboembolic complications of the included studies.**

References, country	AF population		Adverse events during index visit	TEC during index or <30 days
	Included	**Excluded**		
Falk et.al.[1] 1987, U.S.	new-onset AF seen in the ED or on the wards (duration 7 days or less)	congestive HF, heart rate <85 bpm or >175bpm, acute myocardial infarction or unstable angina, pre-excitation syndrome, serum potassium level <3.2 mmol/L, renal impairment (blood urea nitrogen > 29 mmol/L), creatinine concentration >167 mmol/L, severe, acute hypoxia (P02 <55 mmHg), severe metabolic disturbances, acidosis, sepsis or thyrotoxicosis, currently taking digitalis glycosides or AADs	NA	NA
Capucci et.al.[2] 1992, Italy	recent-onset AF (<7days)	age > 75 years, HF > NYHA Class II, HR during AF < 70 beats/min, myocardial infarction or unstable angina pectoris ((< 6 months), pre-excitation syndrome or complete bundle branch block, second- or third-degree atrioventricular or bifascicular block, SSS, potassium < 3.5 mEq/L, renal or hepatic failure, severe hypoxia (partial pressure of oxygen < 55 mmHg), or severe metabolic disturbances or known thyroid dysfunction, digoxin or AAD chronically or <8hours	flecainide group: light-headedness (n=1); pauses >2sec (n=2) amiodaron group: phlebitis (n=2); pauses >2sec (n=2) placebo group: pauses >2sec (n=1)	NA
Capucci et.al.[3] 1994, Italy	recent-onset AF (<7days) (if AF> 72 h only if chronically anticoagulated with warfarin)	age > 75 years, HF > NYHA Class II, HR during AF < 70 beats/min, myocardial infarction or unstable angina pectoris ((< 6 months), pre-excitation syndrome or complete bundle branch block, second- or third-degree atrioventricular or bifascicular block, SSS, potassium < 3.5 mEq/L, renal or hepatic failure and severe hypoxia (partial pressure of oxygen < 55 mmHg), or severe metabolic disturbances or known thyroid dysfunction, digoxin or AAD chronically or <8hours	oral flecainide: pauses >2sec (n=5); atrial flutter before conversion (n=4); junctional rhythm after conversion (n=1); pulmonary edema (n=1); transient visual blurring (n=1) oral propafenone group: pauses >2sec (n=1); atrial flutter before conversion (n=4); junctional rhythm after conversion (n=1); pulmonary edema(n=1) placebo group: pauses >2sec (n=3); atrial flutter before conversion (n=5)	NA
Bellandi et.al.[4] 1996, Italy	paroxysmal AF lasting more than 30 minutes but less than 7 days	angina or clinical signs of HF (dyspnea, pulmonary congestion or systolic blood pressure <90 mmHg), HR <70 beats/min, currently taking digoxin, calcium antagonists or other AADs	propafenone group: bradycardia (<40bpm) after conversion (n=6); pause/SA of 3.4 and 3.8 seconds (n=2); atrial flutter before conversion to SR (n=16); minor digestive side effects (nausea)(n=11); dizziness(n=7) and headache (n=6) placebo group: none	NA

Table S3. (continued)

References, country	AF population		Adverse events during index visit	TEC during index or <30 days
	Included	**Excluded**		
Galve et.al.[5] 1996, Spain	recent-onset AF (<7days)	previous AAD treatment (digoxin included), systolic RR <100mmHg, HR <120bpm, congestive HF (mild cases accepted), severe impairment of left ventricular function, obstructive hypertrophic cardiomyopathy, renal insufficiency, thyroid dysfunction, high degree AV block, SSS, pulmonary fibrosis, hepatic dysfunction, refusal to participate	amiodarone group: hypotension <100mmHg(n=4); NSVT (n=1); phlebitis (n=1) placebo group: hypotension <100mmHg(n=4); vomiting(n=2); atrial flutter (n=1); junctional rhythm (n=1	NA
DAAF trial group [6] 1997, Sweden	recent-onset AF (<7days)	ongoing treatment with digoxin or AAD or calcium channel blockers, SSS, second or third degree AV block without PM, WPW syndrome, HR <60 bpm or >170 bpm, myocardial infarction (<4wks), HD instability, serum potassium <3.5 mEq/L, serum creatinine >300umol/l	digoxin group: bradycardia (n=4); asystole 10 sec (n=1); circulatory distress due to undiagnosed HOCMP(n=1) placebo group: none	NA
Azpitarte et.al.[7] 1997, Spain	all patients with acute AF presenting at the ED	ongoing treatment with AAD, previous embolic event, mean HR <70bpm in AF, symptomatic ischaemic heart disease, dilated or hypertrophic cardiomyopathy, severe hypertension, pre-excitation, hepatic or renal dysfunction, severe pulmonary disease, intraventricular conduction defects, SSS, HD instability	propafenone group: atrial flutter (n=1), hypotension (n=4), pause >2sec (n=1), bradycardia (n=1) placebo group: atrial flutter (n=1)	NA
Boriani et.al.[8] 1997, Italy	recent-onset AF (< 7 days) (if AF> 72 h only if chronically anticoagulated with warfarin)	age > 80 years, HF > NYHA Class II, HR during AF < 70 beats/min, myocardial infarction or unstable angina pectoris ((< 6 months), pre-excitation syndrome or complete bundle branch block, second- or third-degree atrioventricular or bifascicular block, SSS, potassium < 3.5 mEq/L, renal or hepatic failure with severe hypoxia (partial pressure of oxygen < 55 mmHg), or severe metabolic disturbances or known thyroid dysfunction, digoxin or AAD chronically or <8hours	propafenone group: sustained atrial flutter/tachycardia (n=8), pause >2sec (n=1), QRS duration >120ms (n=3), hypotension (n=2), slight hypotension and bradycardia at conversion (n=3) placebo group: sustained atrial flutter/tachycardia (n=7), pauses >2sec (n=3)	NA

Table S3. (continued)

References, country	AF population		Adverse events during index visit	TEC during index or <30 days
	Included	**Excluded**		
Cotter et.al.[9] 1999, Israel	paroxysmal atrial fibrillation <48 h and if they had had at least one previous episode of paroxysmal atrial fibrillation.	severe brady arrhythmia including significant sinoatrial and atrioventricular node disease, hemodynamically unstable, significant chronic lung disease, hepatic failure or active hepatitis, previous recent treatment with amiodarone or known hypersensitivity or significant side effects related to amiodarone, treatment with any class I or III AAD, recent treatment with digoxin or acute myocardial infarction in the previous 7 days.	amiodarone group: sinus bradycardia <50bpm (n=5); phlebitis (n=8) placebo group: sinus bradycardia <50bpm (n=2); phlebitis (n=3); TIA 10hrs after inclusion(n=1); myocardial infarction <24h (n=1)	1 TIA placebo group 10 hours after inclusion
Hohnloser et.al.[10] 2004, Germany	symptomatic AF or AFL of 3- to 48-h duration, BP >90 mmHg systolic and BP <105 mmHg diastolic.	HF NYHA class III/IV; ACS, PCI or ACS within the previous 30 days; cardiac surgery within the last 90 days; history of CVA within the last six months; known WPW syndrome; history of life-threatening ventricular arrhythmias, second or third degree AV block, congenital long QT syndrome, plasma creatinine >1.8 mg/dl; serum potassium <4.0 mEq/l; evidence of digitalis toxicity; concurrent therapy with AAD except beta-blockers, diltiazem, or digoxin not discontinued at least five half-lifes before randomization; and treatment with amiodarone within the last three months.	tedisamil group: bradycardia (17%); injection site burning/pain (17%); first degree AV block (9%); ventricular tachycardia(10%) placebo group: bradycardia (9%); injection site burning/pain (0%); first degree AV block (5%); ventricular tachycardia (2%)	NA
Hassan et.al.[11] 2007, U.S.	new-onset or paroxysmal AF and a rapid ventricular rate (>100 beats per minute over 10 minutes)	History of allergy or adverse reactions to diltiazem or esmolol, cardiogenic shock or heart failure requiring inotropic agents or intubation, pregnancy, lactation, systolic blood pressure less than 80 mm Hg, respiratory failure requiring intubation, ST-elevation myocardial infarction, severe COPD or asthma, chronic/persistent AF, and the inability or unwillingness to provide informed consent	diltiazem group: bradycardia (n=2) esmolol group: hypotension (n=1); wheezing (n=1)	NA
Pluymaekers et.al.[12] 2019, Netherlands	hemodynamic stable, symptomatic patients with AF <36hours	ACS, HF, heart rate <70bpm, pre-excitation syndrome, SSS, history of persistent AF	early cardioversion: heart failure (n=1); bradycardia or hypotension (n=2); tachycardia (n=1) wait-and-see group: heart failure (n=1); bradycardia or hypotension after delayed cardioversion (n=1); tachycardia (n=1)	TIA/ischemic stroke: early cardioversion (n=1), wait-and-see(n=1)

Table S3. (continued)

References, country	AF population		Adverse events during index visit	TEC during index or <30 days
	Included	**Excluded**		
Danias et.al.[13] 1998, U.S.	AF <72hours	concomitant AAD therapy at the time of presentation, performance of a transesophageal echocardiography–guided approach for active cardioversion	NA	NA
Dell'Orfano et.al.[14] 1999, U.S.	primary diagnosis of AF (ICD9 code 427.31), documentation of the arrhythmia by single-channel or 12-lead ECG	patients who were admitted with another diagnosis and had secondary AF, patients who were treated in the ED and released without admission, and patients admitted for AF who did not seek initial treatment in the ED.	NA	NA
Mattioli et.al.[15] 2000,Italy	lone AF with a clinically estimated duration of <6 hours	a history of myocardial infarction, HF, hyperthyroidism, rheumatic heart disease, pulmonary embolism, systemic hypertension, and concomitant AAD therapy at the time of presentation	NA	NA
Mattioli et.al.[16] 2005,Italy	hemodynamically stable patients, hospitalized for an acute episode of lone AF (<6h onset of symptoms)	chronic AF, history of myocardial infarction, heart failure, hyperthyroidism, rheumatic heart disease, pulmonary embolism, systemic hypertension and reduced LV function (ejection fraction<45%), AAD therapy, receiving calcium antagonist or beta-blocker	NA	NA
Geleris et.al.[17] 2001, Greece	consecutive patients with recent onset AF (< 24 h)	hemodynamically unstable, recent ACS, unstable angina, heart rate > 150 bpm, hyperthyroidism, HF, LVH, valvular heart disease, and on AAD at the time of admission	NA	NA
Dixon et.al.[18] 2005, U.S.	a primary diagnosis of AF (essential reason for hospital admission)	AF as a secondary diagnosis	NA	NA
Doyle et.al.[19] 2011, Australia	patients with stable acute AF, AF <48hours	unstable, severe symptoms, need hospitalization, pregnant, or poor candidates for ED procedural sedation	asymptomatic hypotension during procedural sedation (n=1)	none

Table S3. (continued)

References, country	AF population		Adverse events during index visit	TEC during index or <30 days
	Included	**Excluded**		
Perrea et.al.[20] 2011, Greece	AF at the time of presentation, with sudden onset of symptoms due to the dysrhythmia (<48h)	systolic BP <100 mmHg, serum potassium < 3.5 mmol/L, pretreatment with any AAD, known thyroid disease, documented chronic AF, atrial flutter, QTC interval > 440 ms, recent myocardial infarction, severe congestive heart failure (AHA class III and IV), cardiac surgery within the last 6 months, and severe pulmonary disease	NA	NA
Scheuermeyer et.al.[21] 2012, Canada	consecutive patients with AF	referred to the ED for direct admission, if visit was to ED was specifically for OAC monitoring, if <7 days before an ablation, PM insertion, PCI, CABG was performed, sepsis, shock, pneumonia, ACS, HF, pulmonary embolism, COPD, thyrotoxicosis, hypertensive emergency, drug overdose, acute valvular disease, or hypothermia	NA	2 strokes (1 in patient receiving rate control (no CV), and one in the group without acute AF treatment
Lindberg et.al.[22] 2012, Denmark	consecutive patients admitted to hospital with first onset AF	Duration of AF <5 minutes	NA	none during ED visit
Vinson et.al.[23] 2012, U.S.	recent-onset AF (<48 hours)	-	attempted cardioversion: vomiting (n=1); VT (n=2); hypoventilation(n=1) no cardioversion attempted: hypotension (n=2)	2/206 CVA (without OAC)
Choudhary et.al.[24] 2013, Sweden	patients with paroxysmal AF<48hours	thyroid illness, acute IHD, HF, significant valvular heart disease, CHD, history of cardiac surgery or catheter ablation, or on class I/III AADs	NA	NA
Abadie et.al.[25] 2019, U.S.	low-to-moderate risk AF patient	HD instable, severe symptoms, recent syncope, HR >130 despite rate control or MAP <55, physician discretion	NA	

Table S4. **Summary of adverse events during the index visit.**

	Active cardioversion n= 966		**SCV (placebo/rate control) n= 1078**	
	n	%	n	%
light-headedness / dizziness	8	0.83%	0	0%
pauses /sinus arrest	15	1.55%	8	0.74%
phlebitis/injection site burning	30	3.11%	3	0.28%
junctional rhythm	1	0.10%	1	0.09%
bradycardia or hypotension	47	4.87%	22	2.04%
conduction disorders	13	1.35%	3	0.28%
tachycardia/atrial flutter/(NS)VT	45	4.66%	16	1.48%
heart failure / pulmonary edema	3	0.31%	1	0.09%
other non cardiovascular events	20	2.07%	3	0.28%
Stroke/TIA	0	0%	1	0.09%
Acute coronary syndrome	0	0%	1	0.09%

This table includes the 13 studies reporting on adverse events[2-12,19,23].

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PART II

Cardioversion of AF

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, H.J.G.M. Crijns, for the RACE 7 ACWAS Investigators.

* both authors contributed equally

N Engl J Med. 2019;380, 1499-1508.

Early or Delayed Cardioversion in Recent-Onset Atrial Fibrillation

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.)

INTRODUCTION

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 non-teaching 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). 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.

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 CHA_2DS_2–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, cardio- vascular 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.

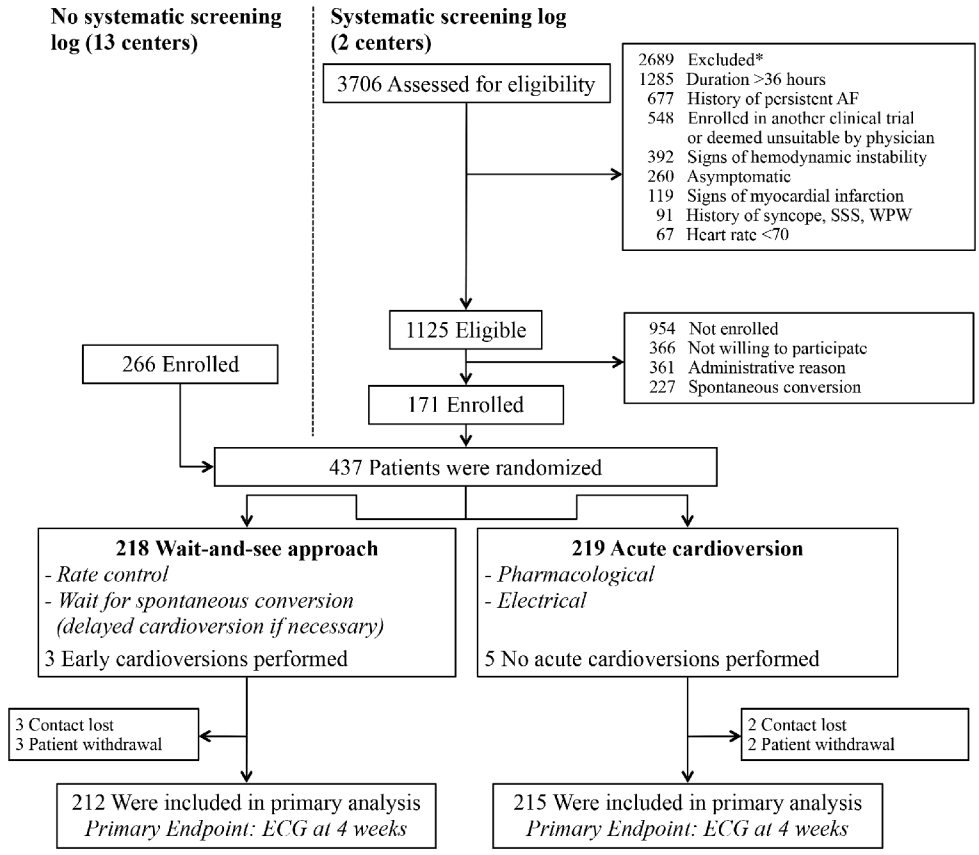


Figure 1. Screening, Randomization, and Follow-up. *In the delayed-cardioversion group, patients received rate-control medication and were discharged when their con-dition was determined to be clinically stable. An outpatient clinic visit was planned for the next day, as close as possi- ble to 48 hours after the onset of symptoms of atrial fibrillation (AF). At this visit, the heart rhythm was reassessed on 12-lead electrocardio- graphy (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 pharmaco- logic or electrical cardioversion, depending on their medical history. SSS denotes sick sinus syndrome, and WPW Wolff–Parkinson–White syndrome.*

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]

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 exact 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 (±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-cardio- version group (including 1 patient with ischemic stroke and 3 with acute coronary syndrome or unstable angina) and 8 in the early

Table 1. **Characteristics of the Patients at Baseline.***

Characteristic	Wait-and-see (n=218)	Acute cardioversion (n=219)
Age (years)	65±11	65±11
Male sex – no.(%)	131 (60 %)	130 (59 %)
Hypertension – no.(%)	118 (54 %)	133 (61 %)
Diabetes – no.(%)	21 (10 %)	25 (11 %)
History of myocardial infarction – no.(%)	24 (11 %)	13 (6 %)
History of ischemic cerebrovascular accident/TIA – no.(%)	12 (6 %)	15 (7 %)
CHA_2DS_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 %)
Dyspnea	56 (26 %)	44 (20 %)
Chest pain	54 (25 %)	44 (20 %)
Heart rate in AF (beats/min) †	123 (101-144)	125 (103-143)
Medication use – no.(%)		
Vitamin K antagonist	34 (16 %)	34 (16 %)
NOAC	56 (26 %)	51 (23 %)
Anti-arrhythmic 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.*

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.

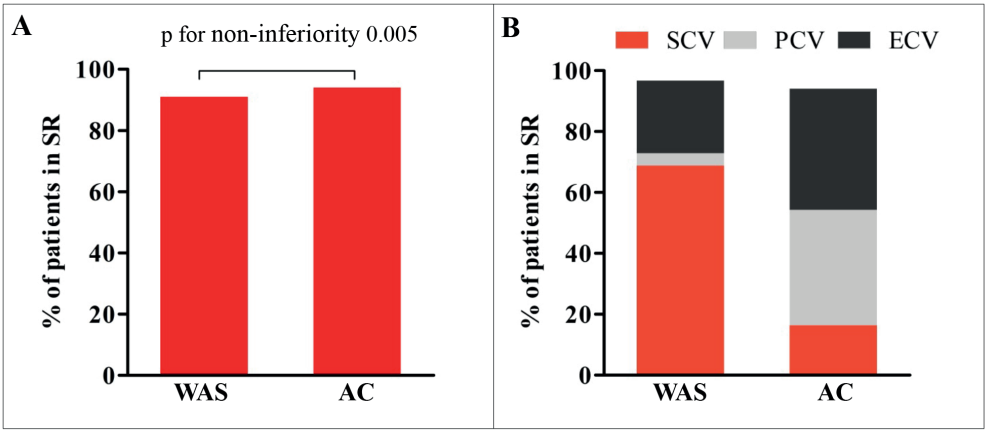


Figure 2. Primary End Point and Distribution of Cardioversion Methods. Panel A *shows the percentage of patients with the primary end point (sinus rhythm at 4 weeks after the index visit) among those who were treated with a wait-and-see approach (delayed-cardioversion group) or early cardioversion.* ***Panel B*** *shows the percentage of patients in sinus rhythm according to the method of cardioversion during the in- dex visit. The index visit included the emergency department visit for all patients and a next-day emergency depart- ment 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.*

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.

Treatment

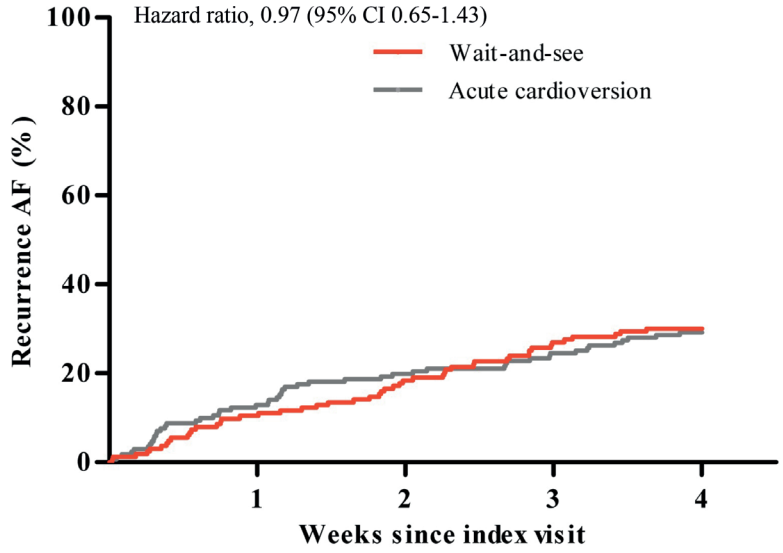
In the delayed cardioversion group, conversion to sinus rhythm within 48 hours occurred spontaneously in 150 of 218 patients (69%) who were receiving rate control medication only and in 61 patients (28%) after delayed cardioversion (9 pharmacologic and 52 electrical) (Fig. 2B). Rate control medication included beta-adrenergic receptor blocking agents (in 155 patients), nondihydro- pyridine 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 patients 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 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.

Table 2. **Cardiovascular complications during index visit and 4 weeks follow-up.**

	Index visit		During 4 weeks follow-up	
	Wait-and-see (n=218)	**Acute cardioversion (n=219)**	**Wait-and-see (n=218)**	**Acute cardioversion (n=219)**
Admission for heart failure – no.	1	1	0	0
TIA/ Ischemic stroke – no.	0	0	1	1
Unstable angina/ACS – no.	0	0	3	3
Bradycardia/ hypotension – no.	1 *	2	2 #	0
Tachycardia – no.	1	1	1 †	0
Side effect medication – no.	0	1	1	0

*The index visit is defined as initial visit including 48 hours visit in the wait-and-see group. * Sinus bradycardia, hypotension and sinus arrest after delayed cardioversion at 48 hours for which hospital admission for rhythm observation. # In one patient, after flecainide infusion, sinus arrest with asystole during 30 seconds occurred, necessitating temporary chest compressions until return of spontaneous circulation. † Wide QRS tachycardia after flecainide infusion.* ***ACS*** *= acute coronary syndrome,* ***TIA*** *= transient ischemic attack.*



No at risk

Wait-and-see	164	147	134	120	114
Acute cardioversion	171	150	138	130	121

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 tele- metric ECG monitoring was available. The hazard ratio is for the delayed- cardioversion group as compared with the early-cardioversion group.*

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.

DISCUSSION

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 cardioversion 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 CHA_2DS_2-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 CHA_2DS_2-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 mentioned. 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 re- mote 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.

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SUPPLEMENTARY FILE

Early or Delayed Cardioversion in Recent-Onset Atrial Fibrillation

SUPPLEMENTARY CONTENTS

RACE 7 ACWAS LIST OF AUTHORS, COMMITTEES AND INVESTIGATORS

Authors

1. H.J.G.M. Crijns , N.A.H.A. Pluymaekers, E.A.M.P. Dudink, J.G.L.M. Luermans
2. J.G. Meeder
3. T. Lenderink
4. J. Widdershoven
5. J.J.J. Bucx
6. I.C. Van Gelder, M. Rienstra
7. O. Kamp
8. J.M. Van Opstal
9. M. Alings
10. A. Oomen
11. C.J. Kirchhof
12. V.F. Van Dijk
13. H. Ramanna
14. J.G.P. Tijssen
15. A. Liem
16. L.R. Dekker
17. B.A.B. Essers

Institutional affiliations

1. Maastricht University Medical Center, Cardiology and Cardiovascular Research Institute Maastricht (CARIM), Maastricht, Netherlands
2. VieCuri Medical Center Noord-Limburg, Cardiology, Venlo, Netherlands
3. Zuyderland Medical Center, Cardiology, Heerlen, Netherlands
4. Elisabeth-TweeSteden Hospital, Cardiology, Tilburg, Netherlands
5. Diakonessen Hospital, Cardiology, Utrecht, Netherlands
6. University Medical Center Groningen, Cardiology, Groningen, Netherlands
7. Amsterdam University Medical Center, location VUmc, Cardiology, Amsterdam, Netherlands
8. Medical Spectrum Twente, Cardiology, Enschede, Netherlands
9. Amphia Hospital, Cardiology, Breda, Netherlands
10. Antonius Hospital, Cardiology, Sneek, Netherlands
11. Alrijne Hospital, Cardiology, Leiderdorp, Netherlands
12. St. Antonius Hospital, Cardiology, Nieuwegein, Netherlands
13. Haga Teaching hospital, Cardiology, The Hague, Netherlands
14. Amsterdam University Medical Center, location AMC, Cardiology, Amsterdam, Netherlands
15. St. Franciscus Gasthuis, Cardiology, Rotterdam, Netherlands
16. Catharina Hospital, Cardiology, Eindhoven, Netherlands
17. Maastricht University Medical Center, Clinical Epidemiology and Medical Technology Assessment, Maastricht, Netherland

Members of the RACE 7 ACWAS trial are as follows: **Writing Committee:** H.J.G.M. Crijns (chair), N.A.H.A. Pluymaekers, E.A.M.P. Dudink, J.G.L.M. Luermans, I.C. Van Gelder, M. Rienstra, J.G. Meeder, J.G.P. Tijssen; **Steering Committee:** H.J.G.M. Crijns (chair), E.A.M.P. Dudink, N.A.H.A. Pluymaekers, J.G.L.M. Luermans, I.C. Van Gelder, A. Liem, C.J. Kirchhof, V.F. Van Dijk, H. Ramanna, J.J.J. Bucx, J.G. Meeder, J. Widdershoven, J.M. Van Opstal, T. Lenderink, L.R. Dekker, M. Alings, O. Kamp, M. Rienstra, A. Oomen, J.G.P. Tijssen, B.A.B. Essers; **Investigators** (all in the Netherlands): *Maastricht University*

Medical Center, Maastricht — H.J.G.M. Crijns, E.A.M.P. Dudink, N.A.H.A. Pluymaekers, J.G.L.M. Luermans, B. Weijs, W. Holvoet; *VieCuri Medical Center, Venlo* — J.G. Meeder, A. Duygun, F. Körver, I.A. Joosen, T. Lankveld, R. Janssen, E.M. Poels, J. Peute, E. Woelders; *Zuyderland Medical Center, Heerlen* — T. Lenderink, T. J. Ansink, R. Pisters, M. Mafi Rad; *Elisabeth-TweeSteden hospital, Tilburg* — J. Widdershoven, Z. Gocmen, M. Scheurwater, J. Verhagen, W. Fitski; *Diakonessen Hospital, Utrecht* — J.J.J. Bucx; *University Medical Center Groningen, Groningen* — I. C. Van Gelder, M. Rienstra, A.H. Hobbelt, R.R. De With, L.B.O. Nguyen; *Amsterdam University Medical Center, location VUmc, Amsterdam* — O. Kamp, M. Ek, B. Koopman, E.J. Verduyn; *Medical Spectrum Twente, Enschede* — J.M. Van Opstal, L. Oldenhof, M. Bader, H. Verheij; *Amphia Hospital, Breda* — M. Alings, J. Huijbregtse, I. Hunze; *Antonius Hospital, Sneek* — A. Oomen, C. Terwisscha van Scheltinga; *Alrijne Hospital, Leiderdorp* — C. J. Kirchhof, L. Kulker; *St. Antonius hospital, Nieuwegein* — V.F. Van Dijk, B. Kara; *Haga Teaching Hospital, The Hague* — H. Ramanna; H. de Lange- van Bruggen; E. Karijodikoro; *St. Franciscus Gasthuis, Rotterdam* — A. Liem, I. Kort; *Catharina Hospital, Eindhoven* — L.R. Dekker, L.M. Rademakers.

Definitions

Cardiovascular complications	Cardiovascular complications leading to hospital admission or emergency department visit (includes: heart failure, ischemic stroke or transient ischemic attack, unstable angina or acute coronary syndrome, symptomatic brady- or tachycardia and hypotension).
Delayed cardioversion	Back-up cardioversion after a wait-and-see period, performed within 48 hours after onset of AF symptoms.
Index visit	Included the emergency department visit for all patients and a next day visit for delayed cardioversion as needed in the wait-and-see patients, all within 48 hours after symptom onset.
Successful rate control	Relief of symptoms and a heart rate of 110 beats per minute or less.

Table S1. **Inclusion and exclusion criteria.**

INCLUSION CRITERIA	EXCLUSION CRITERIA
ECG with atrial fibrillation	Hemodynamic instability (systolic blood pressure < 100mmHg or heart rate > 170 bpm)
Heart rate > 70bpm	Signs of myocardial infarction on ECG
Symptoms most probable due to atrial fibrillation	Presence of pre-excitation syndrome
Duration of symptoms < 36 hours	History of Sick Sinus Syndrome
> 18 years of age	History of unexplained syncope
Able and willing to sign informed consent	History of persistent AF (episode of AF lasting more than 48 hours)
Able and willing to use telemetric rhythm recorder (MyDiagnostick®)	Acute heart failure
	Currently enrolled in another clinical trial
	Deemed unsuitable for participation by attending physician

Figure S1. **Flow chart study design.**

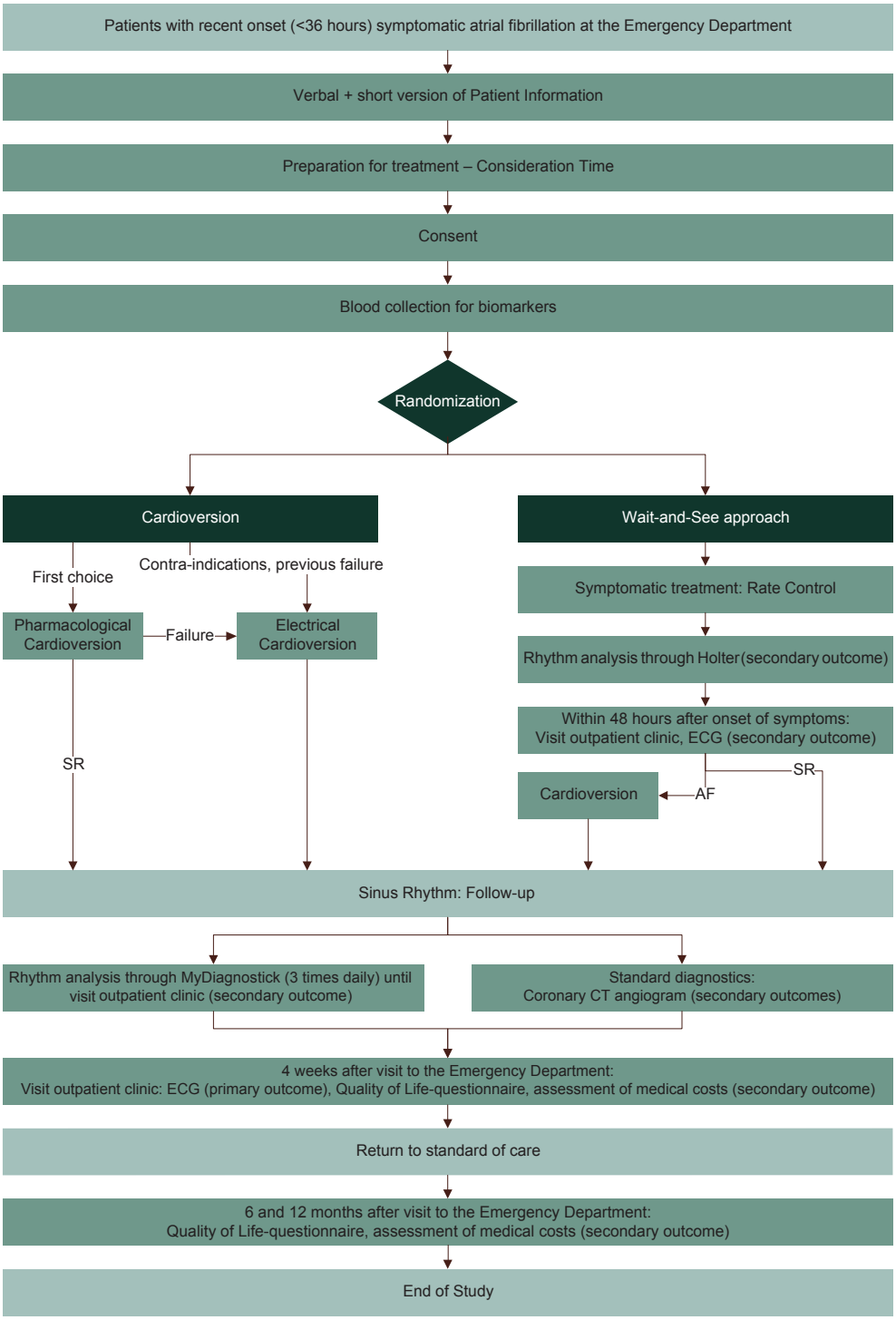


***Table S2*. Overview of prespecified secondary endpoints and analyses and if applicable reason for not including in the manuscript.**

Prespecified secondary endpoints and analysis	Reason for not including in this manuscript
Time to first recurrence of AF in the 4 weeks as well as the 1 year	Time to first recurrence of AF is reported, 1 year will be reported after completion of follow-up
Actuarial curves presenting return of sinus rhythm during the first 48 hours (for wait-and-see group only)	Data is being collected and analyzed and will be reported separately
Total time at Emergency Department	Reported in this manuscript
Time spent in-hospital during index visit (index visit includes 48 hours for all patients)	Same as previous secondary endpoint as we now realize.
AF-burden during 4 weeks	Not available at this time, will be analyzed separately.
Heart rate on MyDiagnostick during 1 month follow-up	Data is being analyzed and will be reported separately
Number of recurrent paroxysms during 1 year	Will be reported after completion of 1 year follow-up
Distribution of AAD, rate control, ablation over time (prescription strategy between groups)	Will be reported after completion of 1 year follow-up
Total number of adverse events associated with index visit	Reported in this manuscript
Emergency department visits for arrhythmias during 1 year follow-up	Will be reported after completion of 1 year follow-up
Cardiovascular hospitalization for stroke/TIA, emboli, bleeding, myocardial infarction, PCI/ CABG, atrial fibrillation/flutter and other arrhythmias, or heart failure during follow up	Reported in this manuscript
All-cause mortality	Reported in this manuscript
Composite of all-cause mortality and CV hospitalization	Reported in this manuscript
PREM (patients reported experience measures)	Will be reported after completion of 1 year follow-up
Quality of life / AFEQT questionnaires	Reported in this manuscript
Total health care consumption	Will be reported after completion of follow-up
Total health care expenditure	Will be reported after completion of 1 year follow-up
Total societal costs	Will be reported after completion of 1 year follow-up
Determinants of spontaneous conversion	Will be reported in a future publication.
Triggers of paroxysmal AF /complaints	Will be reported separately.
Genetic analyses	Will be reported separately.
Complication differences between the use of vitamin K antagonists and NOACs after 1 year follow up	Will be reported after completion of 1 year follow-up

Table S2. **(continued)**

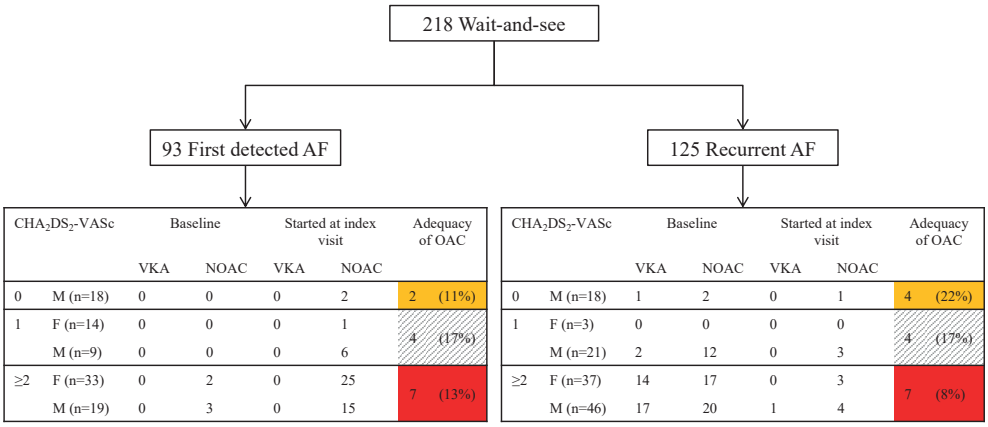
Prespecified secondary endpoints and analysis	Reason for not including in this manuscript
Differences in outcome between different initial conversion strategies (groups concerned are in principle: PCV, ECV, SCV, delayed PCV and delayed ECV and persistent/permanent AF), including the relationships between AF duration, baseline anticoagulation and antithrombotic management during index visit and thereafter, and type of cardioversion	Will be reported in a future publication.
Differences in patients with and without heart failure	Will be reported in a future publication.
Echocardiographic changes after 1 year follow up	Will be reported after completion of 1 year follow-up
Baseline parameters	Reported in this manuscript
Need for rescue rate control medication during index visit, before and after randomization	Reported in this manuscript
Quality of life outcome in relation to rhythm at time of filling in the questionnaire	Will be reported after completion of 1 year follow-up
Variance in outcome parameter associated with gender, time of day (presentation)	Will be reported in a future publication.
Biomarkers, DNA-analysis and ECG parameters	Will be reported in a future publication.
Prediction of AF-recurrence	Will be reported after completion of 1 year follow-up

Table S3. **Post-hoc sensitivity analyses of primary endpoint.**

	Wait-and-see SR/total	Acute cardio-version SR/total	Rate difference	95% CI	p value
A	193/212	202/215	-3.0%	-8.2% to 2.2%	0.005
B	198/218	206/219	-3.2%	-8.5% to 1.8%	0.007
C	193/218	202/219	-3.7%	-9.5% to 1.9%	0.016

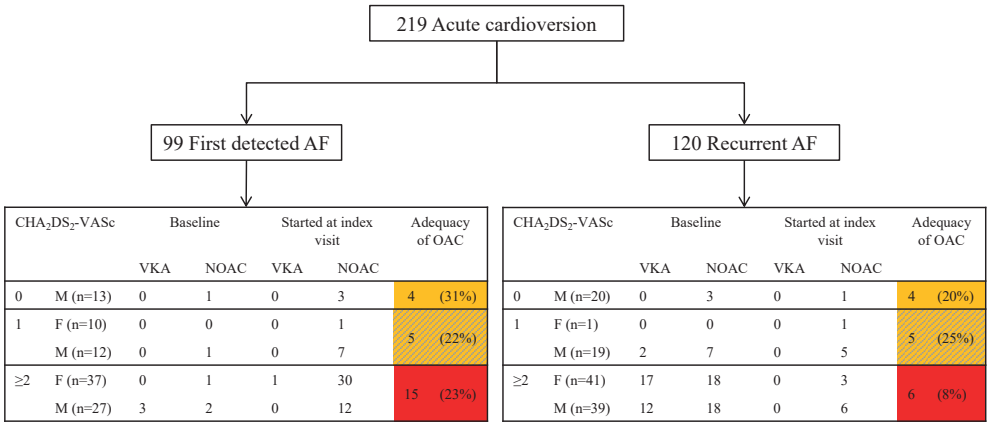
Post-hoc sensitivity analyses were conducted following[17,18]. These analyses included all randomized patients, i.e. also the 10 patients for whom the primary endpoint was unavailable for withdrawal of consent of loss to follow-up. ***A.*** *The patients with missing primary endpoint did not differ from those with known primary endpoint concerning their baseline characteristics in both treatment groups. In addition, the reasons for missing the primary endpoint were the same in both groups. It is then justified to take missing data as missing completely at random and in that case the 427 patients with evaluable primary endpoint represent all cases as randomized (complete case scenario).* ***B.*** *Alternatively, data are missing at random but recorded baseline characteristics used to impute the primary endpoint. Patients with missing primary endpoint had a similar risk of atrial fibrillation compared to patients with an evaluable primary endpoint. The imputation included that all patients with missing primary endpoint contribute to the primary endpoint like complete cases, i.e. show 91% and 94% sinus rhythm at 4-week visit, respectively (all case scenario with imputation based on anticipated clinical outcome).* ***C.*** *Lastly, data are missing at random but patients with missing primary endpoint followed the unlikely scenario of atrial fibrillation at 4-week follow-up (all case scenario with imputation based on worst case primary outcome).*

Figure S2. **Distribution of oral anticoagulation use at baseline and started during the index visit divided by CHA_2DS_2-VASc score and gender.**



CHA_2DS_2-VASc		Baseline		Started at index visit		Adequacy of OAC
		VKA	NOAC	VKA	NOAC	
0	M (n=18)	0	0	0	2	2 (11%)
1	F (n=14)	0	0	0	1	4 (17%)
	M (n=9)	0	0	0	6	
≥2	F (n=33)	0	2	0	25	7 (13%)
	M (n=19)	0	3	0	15	

CHA_2DS_2-VASc		Baseline		Started at index visit		Adequacy of OAC
		VKA	NOAC	VKA	NOAC	
0	M (n=18)	1	2	0	1	4 (22%)
1	F (n=3)	0	0	0	0	4 (17%)
	M (n=21)	2	12	0	3	
≥2	F (n=37)	14	17	0	3	7 (8%)
	M (n=46)	17	20	1	4	



CHA_2DS_2-VASc		Baseline		Started at index visit		Adequacy of OAC
		VKA	NOAC	VKA	NOAC	
0	M (n=13)	0	1	0	3	4 (31%)
1	F (n=10)	0	0	0	1	5 (22%)
	M (n=12)	0	1	0	7	
≥2	F (n=37)	0	1	1	30	15 (23%)
	M (n=27)	3	2	0	12	

CHA_2DS_2-VASc		Baseline		Started at index visit		Adequacy of OAC
		VKA	NOAC	VKA	NOAC	
0	M (n=20)	0	3	0	1	4 (20%)
1	F (n=1)	0	0	0	1	5 (25%)
	M (n=19)	2	7	0	5	
≥2	F (n=41)	17	18	0	3	6 (8%)
	M (n=39)	12	18	0	6	

***AF** = atrial fibrillation, **F**= female, **M** = male, **NOAC** = non-vitamin K oral anticoagulant, **VKA** = vitamin K antagonist, **OAC** = oral anticoagulation. In orange number of patients "overtreated", in red patients "undertreated" concerning anticoagulation management.*

Table S4. **Medication initiated at discharge of the index visit and medication use at 4 weeks follow-up.**

	Initiated at discharge		4 weeks follow-up	
	WAS	**AC**	**WAS**	**AC**
Vitamin K antagonist – no.	1	1	34	37
NOAC – no.	60	69	121	122
Antiplatelet agent– no.	3	1	18	20
Flecainide – no.	6	14	22	50
Amiodaron– no.	1	0	5	3
Sotalol – no.	9	9	34	32
Beta-adrenergic receptor blocking agent – no.	60	33	133	116
Digoxin – no.	5	1	12	4
Non-dihydropyridine calcium channel blocker – no.	6	1	13	8
Dihydropyridine calcium channel blocker – no.	2	1	43	48
Angiotensin-converting enzyme inhibitor – no.	2	1	44	46
Angiotensin Receptor Blocker – no.	2	3	46	60
Statin – no.	2	2	76	86

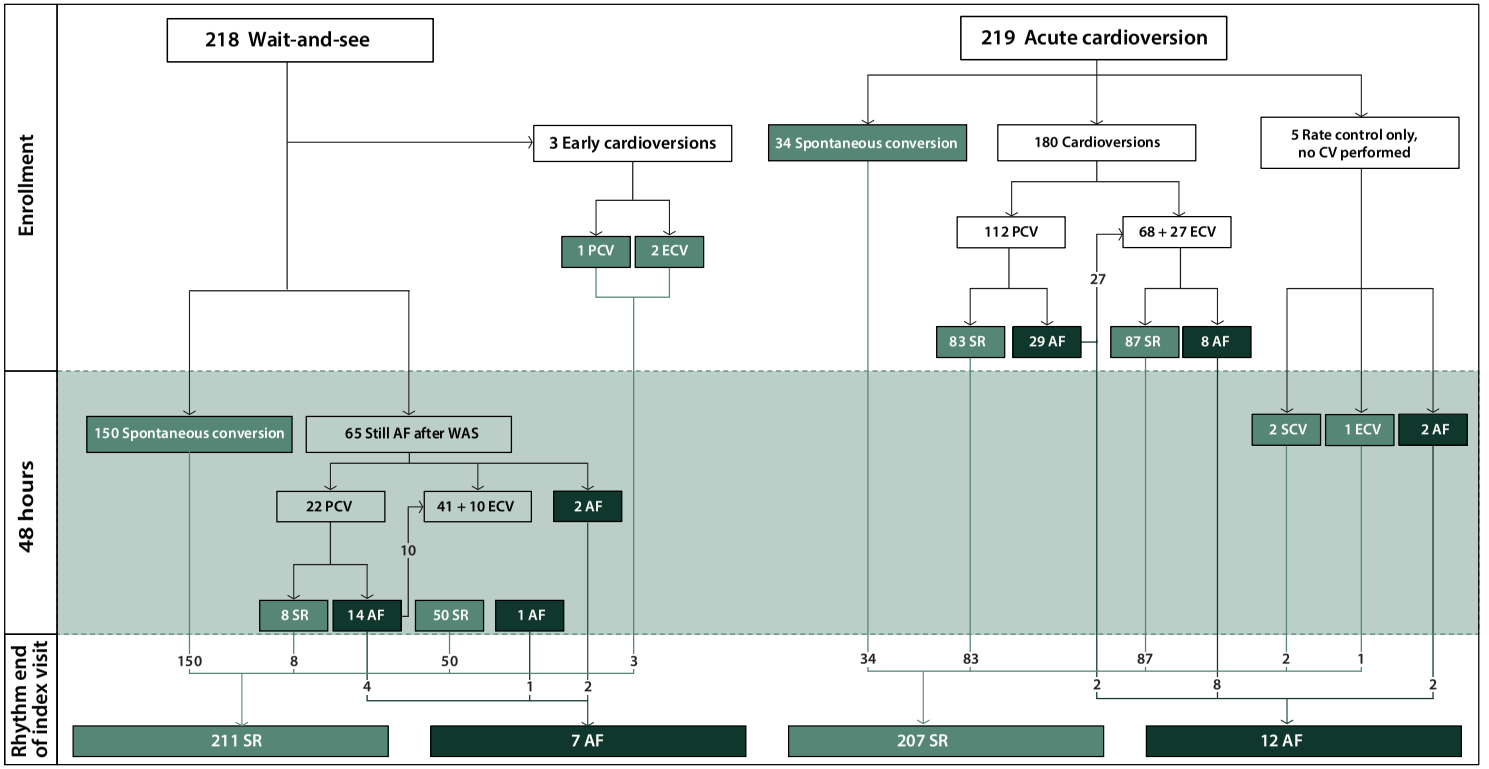
***AC** = acute cardioversion, **NOAC** = non-vitamin K oral anticoagulant, **WAS** = wait-and-see*

Table S5. **Rate control medication given during index visit.**

	Wait-and-see n=218		Acute cardioversion n=219	
Metoprolol – no.(%)	145	(66%)	25	(11%)
Bisoprolol – no.(%)	4	(2%)	1	(1%)
Sotalol – no.(%)	4	(2%)	8	(4%)
Atenolol – no.(%)	1	(1%)	1	(1%)
Nebivolol – no.(%)	1	(1%)	0	(0%)
Digoxin – no.(%)*	13	(6%)	1	(1%)
Verapamil – no.(%)	5	(2%)	0	(0%)
No rate control medication given	43	(20 %)	-	

**One patient received a combination of metoprolol and digoxin.*

Figure S3. **Distribution of Wait-and-see versus Acute cardioversion patients.**



AF *= atrial fibrillation,* ***ECV*** *= electrical cardioversion,* ***PCV*** *= pharmacological cardioversion,* ***SCV*** *= spontaneous conversion,* ***SR*** *= sinus rhythm.*

Table S6. **Serious adverse events listing.**

Serious adverse events within 4 weeks follow up in the Wait-and-see group			
No	**SAE type**	**SAE category**	**SAE description**
1	Requires inpatient hospitalization or prolongation of existing hospitalization	Heart failure*	Spontaneous conversion to sinus rhythm after initiation of rate control with digoxin. Persistent symptoms and signs of heart failure for which hospital admission and start diuretics.
2	Requires inpatient hospitalization or prolongation of existing hospitalization	Tachycardia*	Inadequate rate control after initiated medication, admission to the hospital for further optimization of rate control medication. During admission spontaneous restoration of sinus rhythm.
3	Requires inpatient hospitalization or prolongation of existing hospitalization	Bradycardia/ hypotension*	Sinus bradycardia, hypotension and pauses after delayed electrical cardioversion at 48 hours for which hospital admission.
4	Requires inpatient hospitalization or prolongation of existing hospitalization	Side effect medication	Side effect (NOAC) medication for which observation in-hospital.
5	Requires inpatient hospitalization or prolongation of existing hospitalization	Unstable angina/ ACS	Emergency department visit because of unstable angina, hospital admission.
6	Requires inpatient hospitalization or prolongation of existing hospitalization	Non cardiac	Hospitalisation for appendicitis.
7	Life-threatening	Bradycardia/ hypotension	Sinus arrest after flecainide infusion for delayed cardioversion, 30sec of chest compression, after which return of spontaneous circulation and sinus rhythm.
8	Requires inpatient hospitalization or prolongation of existing hospitalization	Tachycardia	Emergency department visit because of recurrent AF, wide QRS tachycardia after intravenous flecainide administration (most probable aberrant conduction) for which hospital admission for further observation.
9	Requires inpatient hospitalization or prolongation of existing hospitalization	Bradycardia/ hypotension	Emergency department visit because of complaints of dizziness based on total AV block for which PM implantation.
10	Requires inpatient hospitalization or prolongation of existing hospitalization	Unstable angina/ ACS	Emergency department visit for acute coronary syndrome, admission to hospital.
11	Requires inpatient hospitalization or prolongation of existing hospitalization	Non-cardiac	Emergency department visit, admission for treatment of diverticulitis.

Table S6. (continued)

Serious adverse events within 4 weeks follow up in the Wait-and-see group			
No	**SAE type**	**SAE category**	**SAE description**
12	Other significant medical event	Non-cardiac	Diagnosed with Hairy Cell leukemia, Hemoglobin 7.5 mmol/L
13	Life threatening	TIA/ischemic stroke	Ischemic stroke 6 days after index visit.
14	Requires inpatient hospitalization or prolongation of existing hospitalization	Unstable angina/ ACS	Acute coronary syndrome, admission to hospital.
Serious adverse events within 4 weeks follow up in the acute cardioversion group			
No	**SAE type**	**SAE category**	**SAE description**
1	Requires inpatient hospitalization or prolongation of existing hospitalization	Bradycardia/ hypotension*	Before discharge of the index visit patient collapses at the toilet. Admission for observation, no arrhythmias documented. Most probably micturition syncope.
2	Requires inpatient hospitalization or prolongation of existing hospitalization	Side effect medication*	Allergic reaction to amiodaron.
3	Requires inpatient hospitalization or prolongation of existing hospitalization	Tachycardia*	After intravenous infusion of flecainide wide QRS tachycardia with collapse. Admission for observation.
4	Requires inpatient hospitalization or prolongation of existing hospitalization	Bradycardia/ hypotension*	(near)Collapse after emergency department visit (index), hospital admission for observation. No arrhythmias observed, no signs of acute coronary syndrome, differential diagnosis: vasovagal or side effect metoprolol.
5	Requires inpatient hospitalization or prolongation of existing hospitalization	Heart failure*	Randomized to acute cardioversion, due to logistic problems no acute cardioversion possible. Patient was sent home and cardioversion was planned the day after, in the meantime progression of complaints for which earlier return to the emergency department. Patient was admitted with diagnosis of NSTEMI and acute heart failure based on severe mitral valve regurgitation, atrial fibrillation and coronary artery disease.
6	Life-threatening	TIA/ischemic stroke	TIA ten days after electrical cardioversion for AF.
7	Requires inpatient hospitalization or prolongation of existing hospitalization	Unstable angina/ACS	Persisting complaints of angina for which hospital admission.

Table S6. (continued)

Serious adverse events within 4 weeks follow up in the acute cardioversion group			
No	**SAE type**	**SAE category**	**SAE description**
8	Requires inpatient hospitalization or prolongation of existing hospitalization	Non-cardiac	Hospitalization due to airway infection/pneumonia
9	Requires inpatient hospitalization or prolongation of existing hospitalization	Unstable angina/ACS	Emergency department visit because of recurrent AF and complaints of chest pain. After electrical cardioversion resolution of complaints however ECG suggestive for coronary artery disease.
10	Requires inpatient hospitalization or prolongation of existing hospitalization	Non-cardiac	Emergency department visit because of headache and cervical pain, admitted for observation. Treated for sinusitis.
11	Requires inpatient hospitalization or prolongation of existing hospitalization	Unstable angina/ACS	Emergency department visit because of acute coronary syndrome three days after inclusion, hospital admission.

Serious adverse event during the index visit.* ***ACS* *= acute coronary syndrome,* ***AF*** *= atrial fibrillation,* ***ECG*** *= electrocardiogram,* ***TIA*** *= transient ischemic attack,* ***PM*** *= pacemaker.*

Table S7. **(extended) Characteristics of the Patients at Baseline, According to the Assigned Treatment.**

Characteristic	Wait-and-see (n=218)	Acute cardioversion (n=219)
Body mass index (kg/m^2) †	27 (24-30)	27 (24-30)
Hypercholesterolemia – no.(%)	79 (36 %)	83 (38 %)
Coronary artery bypass graft – no.(%)	6 (3 %)	8 (4 %)
Chronic obstructive pulmonary disease – no.(%)	13 (6 %)	16 (7 %)
Chronic renal failure – no.(%)	8 (4 %)	1 (1 %)
First detected AF –no. (%)	93 (43 %)	99 (45 %)
Previous PCV – no.(%) *	44 (21 %)	54 (27 %)
Previous ECV – no.(%) *	53 (26 %)	52 (26 %)
Ablation therapy for AF – no.(%)	13 (6 %)	22 (10 %)
Symptoms – no.(%)		
Exercise-induced fatigue	55 (25 %)	60 (27 %)
Fatigue	63 (29 %)	51 (23 %)
(pre) syncope	19 (9 %)	24 (11 %)
Blood pressure (mmHg) †		
Systolic	130 (117-149)	135 (125-150)
Diastolic	87 (76-96)	90 (80-99)
Medication use – no.(%)		
Antiplatelet agent	27 (12 %)	33 (15 %)
Digoxin	5 (2 %)	3 (1 %)
Flecainide	16 (7 %)	28 (13 %)
Amiodarone	5 (2 %)	3 (1 %)
Sotalol	25 (11 %)	22 (10 %)
Beta-adrenergic receptor blocking agents	84 (39 %)	87 (40 %)
Non-dihydropyridine calcium channel blocker	9 (4 %)	8 (4%)
Dihydropyridine calcium channel blocker	42 (19 %)	46 (21 %)
Angiotensin-converting enzyme inhibitor	41 (19 %)	43 (20 %)
Angiotensin Receptor Blocker	44 (20 %)	60 (27 %)
Statin	73 (34 %)	82 (37 %)

*Plus-minus values are means ± SD. † Median, 25%-75% interquartile range *n=206 Wait-and-see group, n=203 Acute Cardioversion group.* ***AF*** *denotes atrial fibrillation,* ***PCV*** *pharmacological cardioversion,* ***ECV*** *electrical cardioversion*

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J.S. Healey, W.F. McIntyre.

N Engl J Med. 2019;380,1578-1579.

The RACE to treat AF in the emergency department

Atrial fibrillation is an increasingly common reason for presentation to the emergency department, representing nearly 0.5% of all such visits.[1] Appropriate patient care must consider the relief of symptoms, the safety of discharge from the emergency department, the plan for follow-up care, and the use of resources. However, there is great variation in the management of this condition, including the use of cardioversion.[2-5]

Pluymaekers and colleagues[4] now report in the *Journal* the results of the RACE 7 ACWAS randomized noninferiority trial involving 437 patients with recent-onset (<36 hours) atrial fibrillation who presented to 17 emergency departments in the Netherlands. The majority of the patients in this trial had a history of atrial fibrillation, but none had episodes that had lasted more than 48 hours. The patients were randomly assigned to undergo either immediate cardioversion (early-cardioversion group) or a wait-and-see approach with medication (delayed-cardioversion group). The primary end point was sinus rhythm at 4 weeks after the initial emergency department visit.

In the early-cardioversion group, approximately equal numbers of patients underwent electrical or pharmacologic cardioversion, with flecainide being the most commonly used agent in the latter approach. In the delayed-cardioversion group, rate-control medications were used to achieve a heart rate of less than 110 beats per minute and relief of symptoms. Then patients were discharged home, with an outpatient visit scheduled for the following day and a referral for cardioversion (as close as possible to 48 hours after symptom onset) if there had been no resolution of atrial fibrillation.

At the 4-week evaluation, sinus rhythm (as determined on 12-lead electrocardiography [ECG]) was present in 91% of the patients in the delayed-cardioversion group and in 94% in the early-cardioversion group, findings that met the criteria for the noninferiority of the wait-and-see approach. In the delayed-conversion group, 69% of the patients had spontaneous conversion and 28% underwent cardioversion within 48 hours. In the early-cardioversion group, nearly 95% of the patients left the emergency department in sinus rhythm (16% after spontaneous conversion while waiting for the procedure and 78% after cardioversion). The median duration of the stay in the emergency department was 120 minutes in the delayed-cardioversion group and 158 minutes in the early-cardioversion group. There were no significant between-group differences in the patients' quality of life[6] or clinical outcomes at 4 weeks. Among the 335 patients for whom ambulatory ECG recordings were available, nearly a third had a recurrence of atrial fibrillation within 4 weeks, and the time until a first recurrence was similar in the two groups. Fewer than 2% of the patients required hospitalization, 7% required repeat visits to the emergency department because of atrial fibrillation, and cardiovascular complications occurred in 4%.

RACE 7 was a well-designed and well-executed trial with results that can be applied to a sizable population, since 30% of the patients with atrial fibrillation who presented to the emergency department at the two sites that maintained systematic screening logs ultimately were eligible to participate in the trial. Patients were excluded because they presented more than 36 hours after symptom onset (35% of the patients), they had episodes that lasted more than 48 hours (18%), or their condition was hemodynamically unstable (11%), along with multiple other individual and administrative reasons. The findings suggest that rate-control therapy alone can achieve prompt symptom relief in almost all eligible patients, with good quality of life and a low risk of complications, while facilitating rapid discharge from the emergency department. The trial's inclusion criteria identified a large group of patients who had more than a two-thirds chance

of a spontaneous return to sinus rhythm, in whom unnecessary cardioversions were averted. In this pragmatic trial, the wait-and-see strategy reduced the median length of stay in the emergency department to 2 hours, as compared with the 3 to 10 hours expected from observational studies.[2,3,7] However, for these results to be broadly applicable, defined treatment algorithms[7] and access to prompt follow-up are needed, which may not be practical in all settings.

The results of this trial greatly simplify the current controversy regarding the safety of cardioversion between 12 and 48 hours after the onset of atrial fibrillation.[8,9] For most patients with recent-onset atrial fibrillation, the wait-and-see approach may become the preferred strategy, unless they have a history of persistent atrial fibrillation or there are barriers to implementing this approach. Early cardioversion remains an option for patients who have had atrial fibrillation for more than 36 hours if they are receiving long-term anticoagulation, have been classified as low risk on transesophageal echocardiography, or have a low risk of stroke and atrial fibrillation with a duration of 36 to 48 hours.[8] Early cardioversion remains an option for any patient with hemodynamic instability.

Within 1 year after a visit to the emergency department for atrial fibrillation, 5 to 10% of patients will die from any cause, and 10 to 20% will have a stroke, embolism, or myocardial infarction or be hospitalized for heart failure.[10] Although observational studies suggest that sinus rhythm at the time of discharge from the emergency department is associated with an improved prognosis,[5] such reports have confounding factors, since patients in sinus rhythm tend to be healthier. In RACE 7, cardiovascular complications were infrequent and similar in the two trial groups.

Since the early-cardioversion strategy did not significantly increase the rate of sinus rhythm at 4 weeks, it is implausible that such treatment would improve long-term outcomes, a finding that is consistent with the results comparing long-term rate control with pharmacologic rhythm control.[11] However, long-term prognosis can be improved with oral anticoagulation and risk-factor modification,[10,12] which can be initially addressed in the emergency department visit and then effectively managed with routine specialist follow-up.[12,13] Therapy to prevent recurrent hospitalization for atrial fibrillation[11,14] is another key component of long-term care, since most patients who present to the emergency department have recurrent atrial fibrillation.[10,12] The management of atrial fibrillation in the emergency department is not only a sprint to eliminate symptoms and facilitate safe discharge but also the start of a marathon to improve long-term outcomes for patients.

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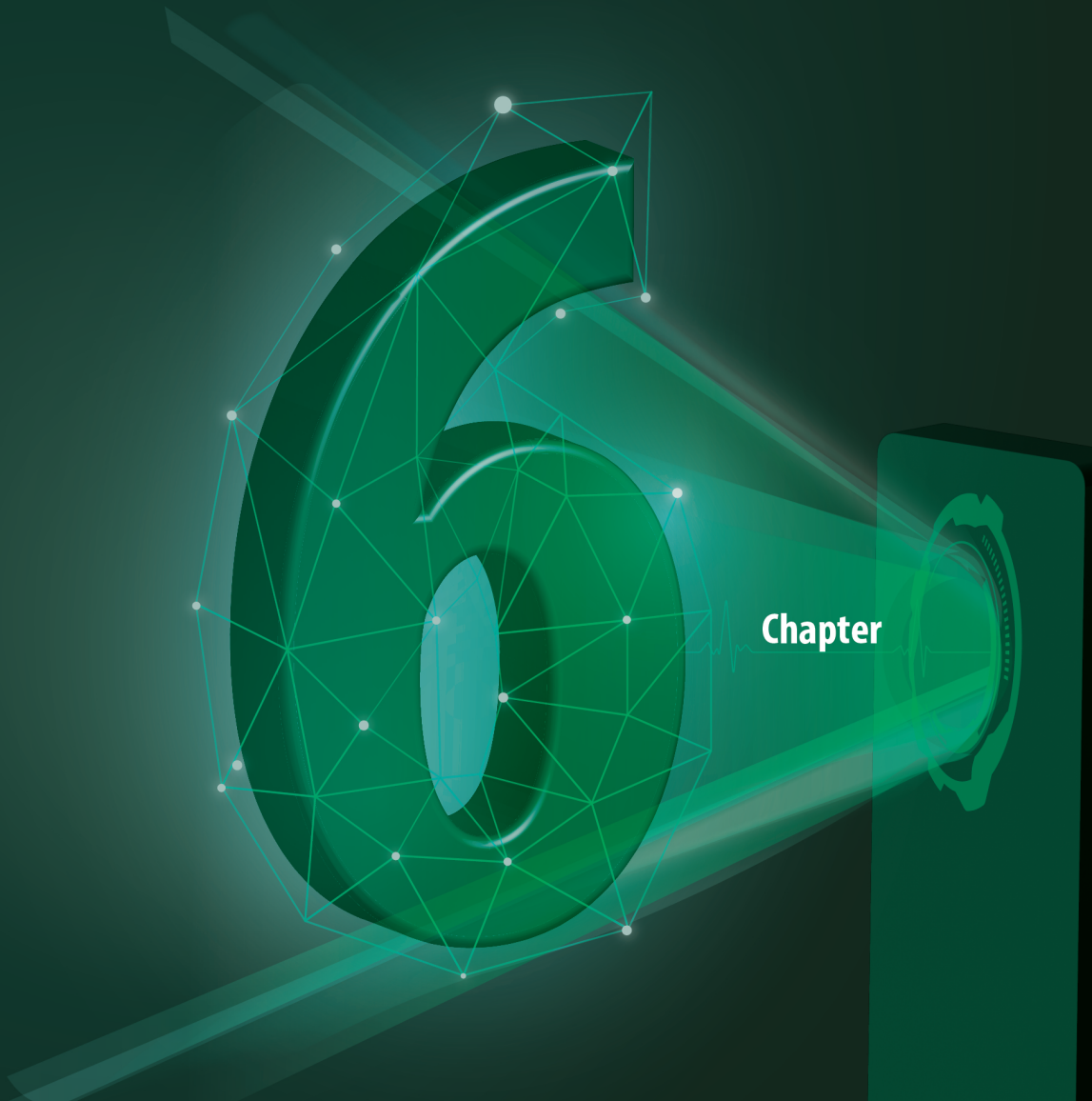
N.A.H.A. Pluymaekers, E.A.M.P. Dudink, H.J.G.M. Crijns.

N Engl J Med. 2019 Jul 25;381(4):387-388.

Early or Delayed Cardioversion in Recent-Onset Atrial Fibrillation. Reply



TO THE AUTHOR:

We thank drs. Boriani and Biffi for their insightful comment that our wait-and-see approach may be enhanced by applying a more stringent patient selection. As many as 69% of patients converted spontaneously <48 hours after onset of atrial fibrillation (AF). Using their selection rules raises this figure only slightly to 80%, indeed reducing delayed cardioversions. However, the number of early cardioversions would increase dramatically. In our population, their algorithm lacks sensitivity and applying it would unduly withhold wait-and-see in 167 out of the 218 (77%) initial wait-and-see patients of whom 65% converted spontaneously. Obviously, we need further studies to improve conversion prediction rules and their impact on practices for acute cardioversion.

We also thank dr. Capucci and colleagues for their interest in our study and agree that adopting a wait-and-see approach precludes observation of 'diagnostic' antiarrhythmic drug responses like conduction abnormalities, ventricular arrhythmias or Brugada ECG.[1] For sure, their approach enhances safety and applicability of pill-in-the-pocket home-cardioversion of recurrent AF.[2] However, patients qualifying for drug treatment nowadays mostly undergo catheter ablation. Immediate patient satisfaction may be hypothesized to be higher with early conversion, but our study shows that it is not maintained after 30 days. Above all, the positive initial reaction of the patients fuels an overly large attention of attending physicians for acute rhythm control, and this may lead to antiarrhythmic overtreatment and distracts from installing appropriate cardiovascular risk management including anticoagulation.[3]

We agree with drs. Vinson and Atzema that cardioversion strategies and local logistics vary greatly,[4] but disagree that the wait-and-see approach increases burden to the emergency department. Our approach undeniably frees up capacity and reduces unplanned cardioversions. In addition, acute AF care pathways can be simplified since the wait-and-see strategy enables planning of cardioversions. The latter may be performed in daycare facilities rather than overcrowded emergency departments. Our findings may feed restructuring processes intended to improve and reduce variance of cardioversion logistics. Also important, in two-thirds of patients a potentially harmful treatment can be avoided. The argument concerning the increased stroke risk with delayed cardioversion does not hold. Regardless of the cardioversion, it is mandatory to assess stroke risk and initiate or continue appropriate anticoagulation indefinitely in all high-risk patients. Unfortunately, this is overlooked too often.[3] In contrast, in low-risk patients cardioversion within 48 hours may be performed safely without anticoagulation.[5]

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N.A.H.A. Pluymaekers, D.K. Linz, M. Rienstra, I.C. Van Gelder, H.J.G.M. Crijns

Lancet. 2020 Sep 26;396(10255):884-885

Emergency department cardioversion of acute atrial fibrillation

TO THE EDITOR:

Stiell et.al. hypothesised that procainamide with eventual DC-shock would be superior to immediate DC-shock in patients with recent-onset atrial fibrillation (AF) at the emergency department, which could not be proven in their study[1]. In contrast, procainamide may enhance cardioversion in *persistent* AF which is more resilient to DC-shock than recent-onset paroxysmal AF[2]. Likewise, the high effectiveness of DC-shock in recent-onset AF precluded finding a difference between paddle positions, which contrasts with a previous study in *persistent* AF[3]. The authors argue that – compared to our delayed cardioversion approach[4] - acute intervention is less burdensome for patients and the hospital because return visits are not needed. However, our strategy was associated with less cardioversions (30% versus virtually all patients), far fewer complications (1,4% versus 20%) and all-in-all less time in the emergency department (2 versus 7 hours). That hospitals cannot offer 24/7 cardioversion services – as the authors maintain - forms a very argument in favour of initial rate control with eventual delayed cardioversion, since it turns disruptive acute care into more efficient planned care, and it also relieves patients who report outside office hours. All of the above indicates a lower burden to patients and hospitals. An important drawback of acute intervention is that it precludes many patients experiencing that their arrhythmia may terminate by itself which may enhance their confidence, reduce anxiety and stimulate self-management. Finally, acute treatments may distract physicians' attention from AF requiring assessment of stroke risk, and treatment of underlying cardiovascular diseases and risk factors contributing to AF[5].

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One year clinical outcome and cost-effectiveness of delayed versus early cardioversion for recent-onset atrial fibrillation. Results from the RACE 7 ACWAS trial.

ABSTRACT

Background

In patients with recent-onset atrial fibrillation (AF) a wait-and-see approach with delayed cardioversion at 48 hours if needed is non-inferior to early cardioversion in achieving sinus rhythm at 4 weeks after the emergency department visit. Our aim is to evaluate the one year clinical outcome, quality of life and cost-effectiveness of the wait-and-see approach with delayed cardioversion compared to early cardioversion.

Methods

Multicentre, non-inferiority trial in which patients presenting at the emergency department with recent-onset AF were randomized to the experimental delayed cardioversion or to reference care of early cardioversion. Clinical outcome and quality of life (SF-36) was evaluated over one year.

Results

407 patients completed the one year follow-up, 202 in the delayed cardioversion group and 205 in the early cardioversion group. Major adverse cardio- and cerebrovascular events occurred in 13% of patients in the delayed cardioversion group vs. 11% in the early cardioversion group. Sinus rhythm was present in 87% of patients in the delayed cardioversion group and in 89% of patients in the early cardioversion group (difference –2%; 95% CI -10.1 to 6.1). The number of patients with one or more recurrent episodes of AF were similar between the groups (56% of patients in the delayed cardioversion group vs. 61% in the early cardioversion group, p=0.352), while the total number of re-visits to the emergency department differed notably (79 re-visits vs. 142 re-visits, respectively). QALY was not significantly different between the groups (0.73 vs. 0.75, p-value 0.126). The mean total costs per year were lower for the delayed cardioversion group as compared to the early cardioversion group (€6356,22 vs. €6980,87; difference -€625; 95% CI -1925 to 602), but not statistically significant.

Conclusion

A wait-and-see approach with delayed cardioversion has fewer cumulative emergency re-visits but otherwise similar clinical outcome and quality of life compared to early cardioversion for patients with recent-onset AF and there is a trend towards lower costs.

INTRODUCTION

The prevalence of atrial fibrillation (AF) and the associated health care costs, continues to increase[1,2]. Recently, we showed that in patients with recent-onset AF a wait-and-see approach with delayed cardioversion at 48 hours if needed is non-inferior to early cardioversion in achieving sinus rhythm at 4 weeks after the emergency department (ED) visit[3]. Applying this wait-and-see approach avoids not only overtreatment with cardioversion in almost 70% of patients, it also allows patients to experience that their arrhythmia may terminate by itself which may enhance self-management. In addition, it enables planning of cardioversions outside the overcrowded ED if a delayed cardioversion is still needed. All of this may contribute to a lower healthcare burden and potentially reduces healthcare costs. Our aim was to evaluate the long-term clinical outcome, cost-effectiveness and quality of life of delayed cardioversion compared with early cardioversion for patients with recent-onset AF.

METHODS

DESIGN AND STUDY POPULATION

A complete overview of the design of the study has been published previously[3,4]. In brief, the RACE 7 ACWAS trial is a multicentre, non-inferiority trial in which patients presenting at the emergency department with recent-onset AF were randomized to the experimental wait-and-see approach with delayed cardioversion or to reference care of early cardioversion. Hemodynamically stable patients with symptomatic recent-onset (<36hours) AF were included. Exclusion criteria were, amongst others, acute heart failure, myocardial ischemia or a history of persistent AF. The study was performed in fifteen cardiology departments in the Netherlands. All participants gave written informed consent. The Institutional Review Board of the Maastricht University Medical Centre+, the Netherlands approved the study and the Institutional Review Boards of all participating sites approved the protocol.

FOLLOW-UP AND ENDPOINTS

Four weeks after inclusion an outpatient clinic visit was planned to evaluate the heart rhythm, and patients were followed over one year. Major adverse cardio- and cerebrovascular events (MACCE), defined as cardiovascular mortality, unplanned hospitalization for thromboembolic events, major bleeding, myocardial infarction, revascularization or heart failure, were evaluated. The number of patients in sinus rhythm at one year, the number of recurrences of AF or other arrhythmias and applications of rhythm control were documented.

The Short-Form 36 (SF-36)[5] questionnaire to assess generic health related quality of life (QoL) was administered at baseline, after four weeks, 6 months and 12 months follow-up. To calculate the cost for medical consumption and productivity loss the Medical Consumption Questionnaire (iMCQ) and Productivity Costs Questionnaire (iPCQ) were used[6]. The Atrial Fibrillation Effect on QualiTy of Life questionnaire (AFEQT)[7], the iMCQ and iPCQ were completed at four weeks, six months and after one year. Quality-adjusted life-years (QALYs) were calculated based on the data obtained with the SF-36 questionnaire using the algorithm of Short Form 6D (SF-6D).

Dutch costs guideline prices were used if available to calculate resource use, otherwise unit prices were obtained from the Dutch Healthcare Authority (NZa)[8] or the financial department of the MUMC+. Lost productivity costs were calculated according to the friction cost approach[9]. Medication prices were obtained from the Dutch Pharmacotherapeutic Compass[10]. All costs are reported in euros at the price level of year 2018. The difference in average costs between delayed cardioversion and early cardioversion divided by the difference in effect between both groups (sinus rhythm at four weeks) was reported as incremental cost-effectiveness ratio (ICER).

STATISTICAL ANALYSIS

Analyses were performed according to the intention-to-treat principle. The chi-square test or Fisher's exact test was used to compare categorical variables, and between group differences for proportions and 95% confidence intervals (CIs) were calculated with the Wald Z method. The Student's t-test was used to compare continuous variables.

Multiple imputation for SF-36, iMCQ and iPCQ values was performed based on predictive mean matching with a first episode, age, gender and CHA2DS2-VASc score as predictive variables. Questionnaires were missing at baseline in 19% of patients, after one month in 34%, 6 months 44% and at 1 year in 42% of patients. Missing values were equally distributed across the two groups. For each missing value, 20 imputations were performed. The costs per QALY were calculated using the one year follow-up data. Since cost data generally have a highly skewed distribution, a non-parametric bootstrap analysis (1000 replications) was performed to estimate uncertainty intervals around the difference in mean costs and to quantify the uncertainty surrounding the incremental cost-effectiveness ratio (ICER). Results of the bootstrap analysis regarding the effectiveness and costs were presented in a cost-effectiveness plane and an acceptability curve. The cost-effectiveness plane is a graphical presentation of four quadrants in which the additional costs and QALY's of the delayed cardioversion are compared to the early cardioversion (standard of care) strategy. The cost-effectiveness acceptability curve shows the probability of delayed cardioversion being more cost-effective compared to standard of care. Baseline utility differences were corrected using a regression based adjustment as recommended by Manca et. al[11]. Four one-way sensitivity analyses were performed to explore the impact of uncertainty on the conclusions of the base-case analysis. To that end, we first used the QALY from a healthcare perspective instead of a societal one, 2) the unadjusted QALY from a societal perspective 3) the rhythm at 4 weeks from a healthcare perspective and 4) a complete case analysis. The bootstrap analysis was performed in Microsoft Excel, all other statistical analyses were performed with IBM SPSS version 25.

RESULTS

PATIENTS

Of the 437 patients included in the study, 407 patients completed the one year follow-up and were included in the analysis, 202 in the delayed cardioversion group and 205 in the early cardioversion group. Reasons for discontinuation were similar between groups (Figure 1). Overall, 165 patients (41%) were female, mean age was 65±11 years and 262 patients (64%) had a CHA_2DS_2-VASc score ≥2. A complete overview of baseline characteristics is reported in Table 1.

OUTCOMES

During a median follow-up of 11 months, major adverse cardio- and cerebrovascular events did not differ between the groups (13% in the delayed cardioversion group vs. 11% in the early cardioversion group, between-group difference, 2 percentage points; 95% CI -4.3 to 8.3). An overview of major adverse events is reported in Table 2.

At one year a 12-lead electrocardiogram (ECG) was performed in 132 patients in the delayed cardioversion group and 115 patients of the early cardioversion group. Sinus rhythm was present in 87% of patients in the delayed cardioversion group and in 89% of patients in the early cardioversion group (difference –2%; 95% CI -10.1 to 6.1). During follow-up the number of patients with one or more recurrent episodes of AF did not differ between the groups (56% of patients in the delayed cardioversion group vs. 61% in the early cardioversion group, p=0.352). In contrast, the total

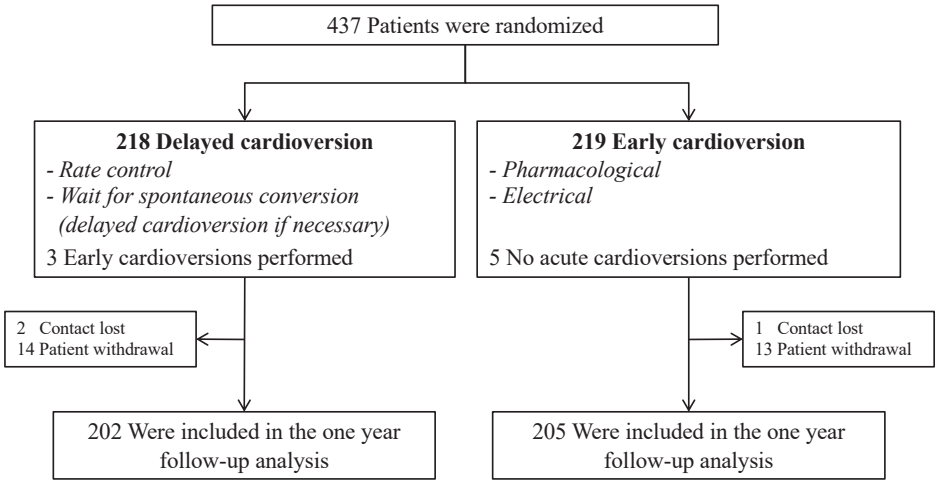

Figure 1. Flowchart.

number of re-visits to the emergency department differed significantly between the two groups (79 re-visits vs. 142 re-visits, respectively). Although numerically lower in the delayed group, the number of patients undergoing single rhythm control therapies did not statistically differ between groups. Cardioversions for AF were applied in 33 patients (16%) in the delayed cardioversion group compared to 44 patients (22%) in the early cardioversion group, 38% vs. 44% of patients received anti-arrhythmic medication, and 7% vs. 14% underwent ablation therapy, all respectively (Figure 2).

Table 1. **Characteristics of the Patients at Baseline, According to the Assigned Treatment.**

Characteristic	Delayed cardioversion (n=202)	Early cardioversion (n=205)
Age (years)	65±11	65±11
Male sex – no.(%)	124 (61%)	118 (58 %)
Body mass index (kg/m^2) †	27 (24-30)	27 (24-30)
Hypertension – no.(%)	113 (56 %)	125 (61 %)
Diabetes – no.(%)	21 (10 %)	24 (12 %)
Hypercholesterolemia – no.(%)	75 (37 %)	76 (37 %)
Myocardial infarction – no.(%)	23 (11 %)	13 (6 %)
Percutaneous coronary intervention – no.(%)	29 (14 %)	19 (9 %)
Coronary artery bypass graft – no.(%)	5 (3 %)	7 (3 %)
Chronic obstructive pulmonary disease – no.(%)	13 (6 %)	13 (6 %)
Ischemic Cerebrovascular accident/Transient ischemic attack – no.(%)	10 (5 %)	15 (7 %)
CHA_2DS_2-VASc score‡– no.(%)		
0	32 (16 %)	32 (16 %)
1	45 (22 %)	36 (18 %)
2	53 (26 %)	55 (27 %)

Table 1. **(continued)**

Characteristic	Delayed cardioversion (n=202)	Early cardioversion (n=205)
≥3	72 (36 %)	82 (40 %)
Chronic renal failure – no.(%)	8 (4 %)	1 (1 %)
First detected AF – no.(%)	86 (43 %)	91 (44 %)
Ablation therapy for AF – no.(%)	11 (5 %)	22 (11 %)
Symptoms – no.(%)		
Palpitations	174 (86 %)	181 (88 %)
Exercise-induced fatigue	52 (26 %)	55 (27 %)
Fatigue	59 (29 %)	47 (23 %)
Dyspnea	51 (25 %)	38 (19 %)
Chest pain	50 (25 %)	41 (20 %)
(pre) syncope	15 (7 %)	22 (11 %)
Blood pressure (mmHg) †		
Systolic	130 (117-148)	135 (125-150)
Diastolic	87 (77-96)	90 (80-99)
Heart rate in AF (beats/min) †	123 (100-144)	125 (104-143)
Medication use – no.(%)		
Vitamin K antagonist	31 (15 %)	34 (17 %)
NOAC	55 (27 %)	51 (25 %)
Antiplatelet agent	26 (13 %)	30 (15 %)
Flecainide	12 (6 %)	22 (11 %)
Amiodaron	6 (3 %)	3 (2 %)
Sotalol	21 (10 %)	18 (9 %)
Beta-adrenergic receptor blocking agents	81 (40 %)	92 (45 %)
Digoxin	5 (3 %)	3 (2 %)
Non-dihydropyridine calcium channel blocker	9 (5 %)	8 (4%)
Dihydropyridine calcium channel blocker	42 (21 %)	44 (22 %)
Angiotensin-converting enzyme inhibitor	38 (19 %)	39 (19 %)
Angiotensin Receptor Blocker	44 (22 %)	59 (29 %)
Statin	72 (36 %)	81 (40 %)

*Plus-minus values are means ± SD. † Median, 25%-75% interquartile range. *n=206 Wait-and-see group, n=203 Acute Cardioversion group. AF denotes atrial fibrillation, **NOAC** non-vitamin K oral anticoagulant, **PCV** pharmacological cardioversion, **ECV** electrical cardioversion. ‡ The CHA2DS2-VASc score is a measure of the risk of stroke in patients with AF, 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 >75 years are assigned two points.*

Table 2. **Major adverse cardio- and cerebrovascular events during one year follow-up.**

	delayed cardio-version (202)	early cardiover-sion (205)	p-value
Mortality			
All-cause mortality	1 (0.5%)	0 (0%)	0.496
Cardiovascular mortality	0 (0%)	0 (0%)	NA
Cardiovascular hospitalization			
Admission for heart failure – no.	3 (1.5%)	2 (1.0%)	0.684
Thromboembolic events – no.	4 (2.0%)	2 (1.0%)	>0.999
ACS/revascularization – no.	10 (5.0%)	8 (3.9%)	0.607
Tachycardia – no.	2 (1.0%)	3 (1.5%)	0.665
Bradycardia – no.	3 (1.5%)	3 (1.5%)	>0.999
Major bleeding – no.	1 (0.5%)	3 (1.5%)	0.623
Other – no.	5 (2.5%)	5 (2.4%)	0.981
Non cardiovascular hospitalization	12 (5.9%)	12 (5.9%)	0.970

Major adverse events during one year follow-up. Table presents single patients experiencing one or more events. If a patient experiences more than once the same event, this was counted as one in this table. ***ACS*** *= acute coronary syndrome.*

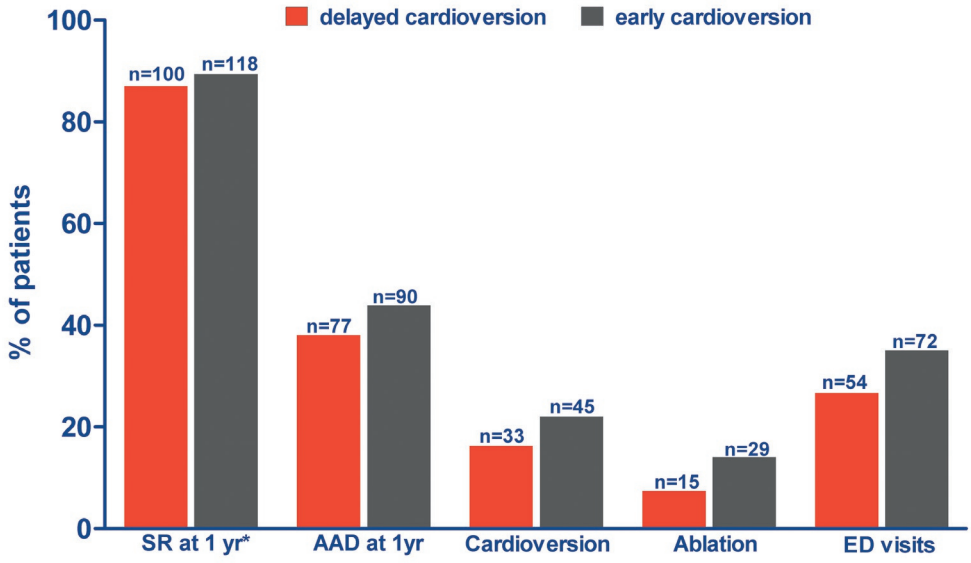

Figure 2. Rhythm control therapies and ED visits within one year. ** based on n=167 for the delayed cardioversion and n=178 for the early cardioversion group due to missing data*

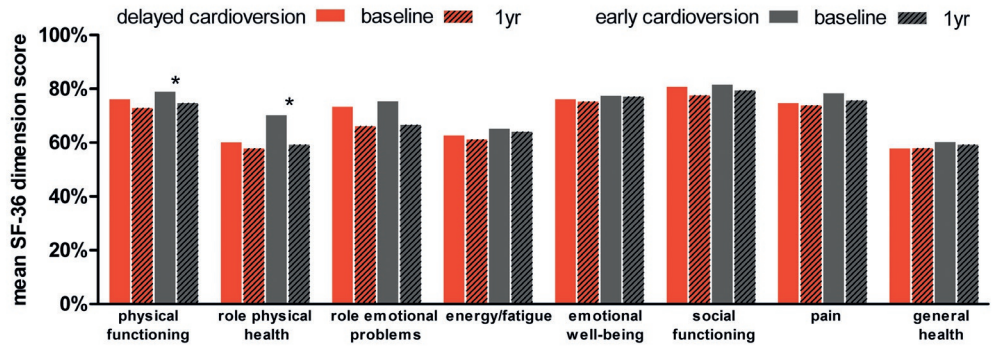

Figure 3. Score on the six domains of the SF-36 questionnaire.

QUALITY OF LIFE AND COSTS

The mean score on the eight domains of the SF-36 (physical functioning, pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions) for baseline and at 1 year follow-up are presented in Figure 3. At baseline, the mean utility score was lower in the delayed cardioversion group compared to the early cardioversion group (0.74 vs. 0.78, p-value 0.003), while the QALY was not significantly different between the groups (0.73 vs. 0.75, p-value 0.126). For the delayed cardioversion group there was no significant difference over time, in the early cardioversion group patients reported significantly lower on the domains physical functioning and limitations physical health at one year compared to baseline (76.0% vs. 72.9% and 60.1% vs. 57.8%, respectively).

The base case analysis compared the incremental costs and QALY for a patient in the delayed cardioversion group with early cardioversion (standard care) from a societal perspective with a time horizon of 1 year. The mean costs for the index treatment for the delayed cardioversion was €475,67 (± 15,3) and for the early cardioversion €466,94 (± 9,58) (Table 3). The mean total costs per year were lower for the delayed cardioversion group as compared to the early cardioversion group (€6356,22 vs. €6980,87; differences -625; 95% CI -1925 to 602), but not statistically significant. The cost-effectiveness plane, Figure 4, showed that 84% of all the ratios were situated in the quadrant where the delayed cardioversion strategy is cost saving but also less effective.

The sensitivity analysis showed the robustness of the findings compared to the base case analysis with the majority of the ICER falling in the quadrant where delayed cardioversion saves costs without a clinically significant loss in effectiveness. This is further supported by the results of a complete case analysis and a societal and healthcare perspective analysis with adjustment of QALY for the baseline difference were performed (Table 4).

Table 3. **Costs during one year follow-up according to the assigned treatment.**

	Unit price	Delayed cardioversion		Early cardioversion		Cost difference (WAS-AC)	
		Volume (SD)	Mean costs (SD)	Volume (SD)	Mean costs (SD)	Mean cost difference	Bootstrapped (2.5^{th};97.5^{th} CI)
Index treatment							
ED visit	€266,04	1.2871	€347,90 (6.93)	1.000	€266,04 (0)	76	(63; 90)
Rate control	€2,67	0.7822	€2,03 (0.06)	0.1268	€0,33 (0.05)	2	(2; 2)
PCV	€42,11	0.0594	€2,5. (0.57)	0.3805	€16,11 (1.16)	-14	(-16; -11)
PCV +ECV	€392,37	0.0446	€17,06 (4.71)	0.1220	€47,13 (7.48)	-29	(-47; -13)
ECV	€350,26	0.1881	€64,08 (8.04)	0.3220	€112,85 (8,96)	-49	(-70; -24)
Admission	€508,45	0	€0 (0)	0.0049	€2,56 (2.08)	-3	(-7; 0)
ECG	€23,62	2.000	€47,25 (0)	1.000	€23,62 (0)	24	(24; 24)
Total index treatment			*€475,67 (15,30)*		*€466,94 (9,58)*	*9*	*(-26; 44)*
Follow-up health care							
Inpatient care							
Echocardiography	€136,61	0.5891	€80,45 (3,83)	0.6146	€ 83,84 (3,94)	-3	(-14; 7)
Coronary angiogram	€3.274,39	0.0198	€64,92 (26,29)	0.0488	€ 160,63 (40,20)	-96	(-189; -1)
Ablation	€11.216	0.0891	€1.008,31 (219,15)	0.1512	€1704,11 (247,79)	-696	(-1.299; -52)
ED visits	€266,04	0.3911	€103,89 (11,57)	0.6927	€185,06 (18,55)	-81	(-125; -38)
Ambulance transport	€528,99	0.4338	€227,51 (28,32)	0.5819	€308,05 (32,79)	-81	(-167; 5)
Hospitalizations days	€488,93	1.2129	€618,17 (116,32)	1.4488	€ 731,74 (187,64)	-114	(-550; 284)
Rehabilitation facility	€472,49	0.4517	€ 216,83 (119,05)-	0.5867	€216,83 (119,05)	-58	-385 ; 265
Other healthcare facility	€310,21	0.0480	€7,05 (3,34)	0.0511	€7,59 (3,13)	-1	(-9; 8)
Outpatient care							
Outpatient clinic	€93,47	5.7985	€540,64 (35,93)	5.7416	€534,77 (37,26)	6	(-102; 106)
General practitioner	€33,89	5.6803	€192,78 (10,20)	5.9621	€201,76 (11,02)	-9	(-38; 21)

Table 3. (continued)

	Unit price	Delayed cardioversion		Early cardioversion		Cost difference (WAS-AC)	
		Volume (SD)	Mean costs (SD)	Volume (SD)	Mean costs (SD)	Mean cost difference	Bootstrapped (2.5^{th};97.5^{th} CI)
Social worker	€66,77	0.5646	€37,72 (8,37)	0.5228	€34,49 (7,33)	3	(-18; 24)
Physiotherapist	€33,89	7.0669	€239,91 (27,32)	9.1562	€308,67 (31,91)	-69	(-152; 20)
Occupational therapist	€33,89	0.4380	€14,73 (3,96)	0.4440	€15,14 (3,81)	0	(-11; 10)
Speech therapist	€33,89	0.0501	€1,68 (1,23)	0.0339	€1,14 (0,66)	1	(-2; 4)
Dietician	€34,92	0.6480	€22,91 (3,59)	0.6437	€22,49 (3,52)	0	(-9; 10)
Homeopath	€33,89	0.4190	€14,28 (3,69)	0.3742	€12,61 (3,73)	2	(-9; 12)
Psychologist	€65,74	0.9015	€59,48 (11,25)	0.8106	€53,54 (10,06)	6	(-24; 35)
Occupational physician	€53,41	0.6056	€32,40 (5,37)	0.3770	€20,15 (3,89)	12	(0; 25)
Domestic help	€20,54	4.8296	€98,32 (23,17)	8.3784	€168,91 (74,24)	-71	(-244; 53)
Care home	€172,56	0.2104	€36,14 (13,78)	0.1016	€17,98 (9,15)	18	(-15; 51)
Nursing home	€172,56	0.0140	€2,52 (6,47)	0.1797	€ 31,86 (21,75)	-29	(-83; 16)
Hospital (day)	€286,58	2.5528	€731,56 (96,68)	2.5728	€738,27 (84,37)	-7	(-275; 236)
Rehabilitation (day)	€157,16	0.1669	€26,69 (14,85)	0.0774	€12,06 (8,88)	15	(-18; 49)
Psychiatry facility (day)	€115,04	0.0810	€9,29 (5,64)	0.0411	€4,82 (4,38)	4	(-12; 19)
Other facility (day)	€147,91	0.7203	€105,58 (34,81)	0.6413	€94,23 (34,81)	11	(-89; 109)
Non-health care							
Productivity loss (hours)	€35,69	36.8177	€1.375,12 (207,91)	19.2124	581,62 (102,63)	794	(359; 1.283)
Informal productivity loss (hours)	€14,38	30.5722	€440,45 (57,30)	21.0269	€301,27 (51,43)	139	(-21; 284)
Total healthcare related costs			**€ 4.952,35 (364,09)**		**6.206,13 (423,95)**	**-1.254**	**(-2.306; 221)**
Total costs			**€6.356,22 (454,57)**		**€6.980,87 (438,38)**	**-625**	**(-1.925; 602)**

Multiple events per patients

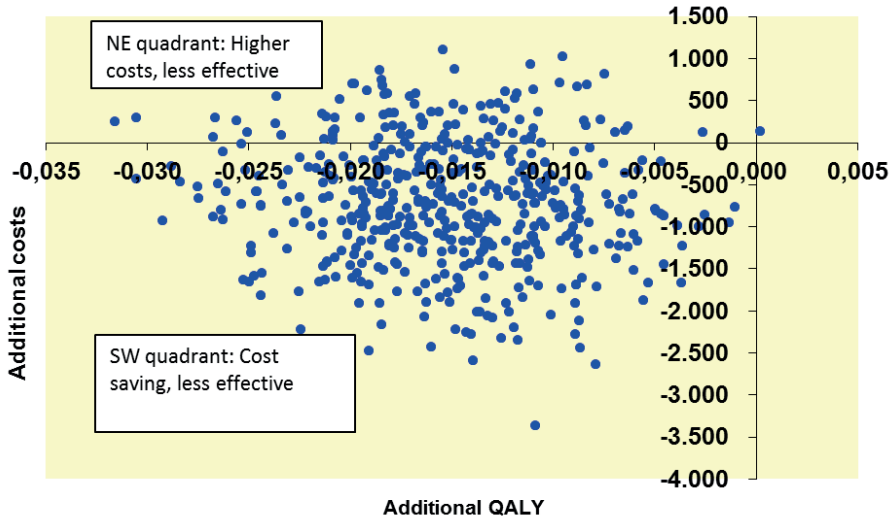

Figure 4. Cost-effectiveness plane. *Showed that 84% of all the ratios were situated in the quadrant where the delayed cardioversion strategy is cost saving but also less effective.*

DISCUSSION

The RACE 7 ACWAS trial is the first trial to investigate the long term clinical outcome and cost-effectiveness of a wait-and-see approach with delayed cardioversion for recent-onset AF. It shows that there is no difference in one year clinical outcome concerning major adverse cardio- and cerebrovascular events between delayed cardioversion and early cardioversion for patients with recent-onset AF. Also the number of patients in sinus rhythm at the end of follow-up was comparable between the groups, despite numerically more rhythm interventions in the early cardioversion group. In the large majority of patients, the delayed cardioversion strategy was cost-saving without negatively affecting clinical outcome and quality of life. These data may inform management pathways for acute AF patients concerning patient-outcomes and cost-effectiveness.

Delaying cardioversion was not associated with an excess of major adverse events. These occurred in 13% and 11% of patients in delayed and acute cardioversion, respectively, which is in line with previous trials in recent-onset AF[12,13]. One would anticipate more strokes in the early cardioversion group because of active cardioversion, but this seemed prevented by appropriate anticoagulation therapy[14,15]. Our results suggest that the difference in approach towards management of recent-onset AF does not impact long term outcome. Notably, recent studies showed that early rhythm control may be beneficial but those studies dealt with early initiated chronic rhythm control in ambulatory AF patients rather than early rhythm control in acute AF[16,17]. Therefore we believe studies are not at odds but may complement each other since delayed cardioversion provides information on spontaneous conversion which may inform type of early rhythm control including type and timing of ablation. The number of patients in sinus rhythm after one year was similar in both groups, and the overall 1-year progression rate from paroxysmal to persistent or permanent AF in this study was the same and moderate (8%)[13,18,19]. Considering the prevalence of factors contributing to AF progression this is what one would expect[12]. The absence of difference in AF progression was more remarkable considering the higher application of rhythm interventions in the early cardioversion group.

Applying a wait-and-see approach allows patients to experience that their arrhythmia may terminate spontaneously. Considering the recurrent nature of the disease this could reduce repeat visits to the ED. In this study we observed less ED visits in the wait-and-see group although not statistically significant. One explanation for this could be that patients in the early cardioversion group had the same information at inclusion on self-terminating AF and how to deal with it, which may have affected the number of re-visits in case of recurrent AF. We hypothesised that if patients experience their arrhythmia terminates spontaneously this would improve their long-term quality of life. But remarkably, at one year there was no significant difference between the groups. Whether the lower quality of life score in the delayed group at baseline played a role here we cannot tell. Long-term rhythm control therapy by medication[20] or catheter ablation may improve quality of life in patients with recent-onset AF[21], and this being undertaken more in the early group may have abolished quality of life differences between groups.

Delayed cardioversion approach allows planning of cardioversion outside the overcrowded ED, in case a cardioversion appears unavoidable, which reduces time and costs of an acute management strategy. However, in our study we showed that costs did not differ significantly between the groups. A possible explanation for this could be that we did not account for duration of ED visits which would favour a delayed cardioversion approach. Another reason could be that more PCVs were performed in the early cardioversion group which is relatively cheap. ECV is a relatively expensive procedure and, dependent on local routines, requires the involvement of nurses, an anaesthesiologist and a cardiologist or emergency physician. Further refinement of the delayed cardioversion approach should focus on optimizing the logistic pathway with introduction of remote heart rhythm assessment which can prevent repeat visits to the ED and thereby reduce costs. This remote heart rhythm assessment can also identify the optimal cut-off to perform a delayed cardioversion approach since spontaneous conversion can occur up till 7 days or even later.

In conclusion, a wait-and-see approach with delayed cardioversion has similar clinical outcome and quality of life compared to early cardioversion for patients with recent-onset AF and there is a trend towards lower costs.

Table 4. **Sensitivity analyses.**

	Δ Effect	**Δ Costs**	**ICER**	**Distribution cost-effectiveness plane (quadrant: % ratio's)***			
				NE	SE	SW	NW
Base Case QALY adjusted*	-0.0151	-€809	€54.050	0%	0%	84%	16%
Health care perspective	-0.0151	-€1300	€86.834	0%	0%	98%	2%
QALY unadjusted societal perspective	-0.0150	-€809	€53.553	0%	6%	81%	13%
Sinus rhythm 4 weeks healthcare perspective	-0.04	-€94	€2.626	2%	6%	68%	24%
Complete case	-0.012	-€725	€58.870	1%	11%	75%	15%

**NE (north east quadrant): WAS more effective and more costly compared to standard; SE (southeast quadrant): WAS more effective and less costly compared to standard: dominant SW (southwest quadrant): WAS less effective and cost saving compared to standard; NW (northwest quadrant): WAS less effective and more costly compared to standard: inferior*

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PART III

Follow-up after cardioversion for AF

N.A.H.A. Pluymaekers, E.A.M.P. Dudink, L. Boersma, Ö. Erküner, M. Gelissen, V. van Dijk, M. Wijffels, T. Dinh, K. Vernooy, H. JGM Crijns, J. Balt, J. G.L.M. Luermans.

Pacing Clin Electrophysiol. 2018;41:1336-1340.

External electrical cardioversion in patients with cardiac implantable electronic devices: is it safe and is immediate device interrogation necessary?

ABSTRACT

Background

Atrial tachyarrhythmias are common in patients with cardiac implantable electronic devices (CIEDs). Restoration of sinus rhythm by external electrical cardioversion (eECV) is frequently used to alleviate symptoms and to ensure optimal device function.

Objectives

To evaluate the safety of eECV in patients with contemporary CIEDs and to assess the need for immediate device interrogation after eECV.

Methods

We conducted a retrospective observational study of 229 patients (27.9% female, age 69±10years) with a CIED (104 pacemakers, 69 implantable cardioverter defibrillators, 56 biventricular devices) who underwent eECV between 2008 and 2016 in two centres. Data from device interrogation before eECV, immediately afterwards, and at first follow up (FU) after eECV were collected. CIED related complications and adverse events during and after eECV were recorded.

Results

No significant differences between right atrial (RA) and right ventricular (RV) sensing or threshold values before eECV, immediately afterwards or at FU were observed. A small yet significant decrease was observed in RA and RV impedance immediately after eECV (484 vs. 462ohms, $p<0.001$ and 536 vs. 514ohms, $p<0.001$ respectively). The RV impedance did not recover to the baseline value (538 vs. 527 ohms, $p=0.02$). Impedance changes were without clinical consequences. No changes in LV lead threshold or impedance values were measured. No CIED related complications or adverse events were documented following eECV.

Conclusion

External ECV in patients with contemporary CIEDs is safe. There seems to be no need for immediate device interrogation after eECV.

Keywords

External ECV, CIED, safety, immediate device interrogation.

INTRODUCTION

Atrial tachyarrhythmias, especially atrial fibrillation (AF), are common in patients with cardiac implantable electronic devices (CIEDs)[1,2]. Restoration of sinus rhythm, by means of electrical cardioversion (ECV), is a frequently used strategy to alleviate symptoms as well as to prevent adverse device reactions and to enable optimal device response. Although external ECV is a well-established and safe treatment strategy in the general AF population [3,4], in patients with a CIED it often remains a cause of concern [1,5]. This is mainly based on older reports describing lead and/or device malfunction caused by for instance energy shunting from the device to unipolar leads or paddle positions close to the pulse generator [6-11]. Nowadays, the use of biphasic shock waveforms for ECV allows reduction of the applied amount of energy and also the use of bipolar leads seems to be an advantage [6,12]. The 2010 ESC guidelines recommended immediate device interrogation after external ECV to confirm normal device function[5], however in the revised guidelines (2016) no recommendation is made on this specific topic[4]. The aims of this study were to confirm our hypothesis that external ECV in patients with contemporary CIEDS is safe and to evaluate whether immediate device interrogation after external ECV is necessary.

METHODS

Setting

We conducted a retrospective observational study of all patients with a CIED who underwent external ECV between 2008 and 2016 in the St. Antonius Hospital (Nieuwegein, The Netherlands) and the Maastricht University Medical Center (Maastricht, The Netherlands). The Medical Ethical Committees of both centers approved the study.

Study population and data collection

All consecutive patients aged 18 years or older with a CIED who underwent external ECV for any atrial arrhythmia between January 2008 and December 2016 were included. Baseline demographics, medical history, medical therapy prior to ECV and electrocardiogram (ECG) were obtained from patients records. The following device specifics were documented: implantation records (implantation date, type of device, manufacturer), data from device interrogation (threshold, sensing and impedance values, lead and/or device malfunction, battery problems) before ECV, immediately afterwards (within two hours after ECV), and at the first follow up interrogation after ECV in the outpatient clinic. Furthermore, ECV records (indication for ECV, applied shock form, number of shocks, applied amount of energy, paddle position, heart rhythm post ECV, ECV related complications) were collected. The primary endpoint was defined as the occurrence of any CIED related complications or adverse events during or after external ECV. CIED related adverse events were predefined as lead malfunctions (sensing problems, significant increase of pacing threshold, transient loss of capture immediately after ECV, notable difference in lead impedance (<200 Ohm or >2000 Ohm), any shock events or device malfunctions (power-on-reset, erroneous programming, and battery problems).

Statistical analysis

Continuous data are reported as mean ± standard deviation (SD), categorical data as number of patients (percentage). Paired samples T-test were used to evaluate differences in sensing, impedance and threshold values before cardioversion, immediately afterwards and at follow up. Statistical significance is presumed for $p<0.05$. Analyses were performed using IBM SPSS statistics version 23 (IBM Corp., Armonk, NY, USA).

RESULTS

We analysed 229 external ECVs in 203 patients (27.9% female, mean age 69±10 years). Baseline characteristics are presented in Table 1. All patients without contra-indications for anticoagulation use were on oral anticoagulation (OAC) therapy (99.1%). Device and cardioversion parameters are presented in Table 2., AF was the most frequent reason for ECV (77.3%), followed by atrial flutter (21.0%), and atrial tachycardia (1.7%). One hundred and four ECVs were performed in patients with a pacemaker, 69 in patients with an implantable cardioverter defibrillator (ICD) and 56 in patients with a biventricular PM or ICD. The median duration from (last) device implantation till ECV was 17.6 months (Range 0-157). Three patients had an ECV within a month after implantation. ECVs were performed using synchronized biphasic shock waveforms in all patients. In 1.3%, internal cardioversion was initially attempted, followed by external ECV in case of no success. An anteroposterior paddle position was the preferred position (87.9%), followed by the anterolateral position (12.1%). Restoration of sinus rhythm was achieved in 97.4% with a mean cumulative energy of 192± 108Joules.

Table 1. **Baseline characteristics of patients with CIEDs undergoing ECV (n=229).**

Age (years)	**69**	**± 10**
Female	64	(27.9%)
Hypertension	124	(54.1%)
Diabetes	40	(17.5%)
COPD	23	(10.0%)
OSAS	16	(7.0%)
History of coronary artery disease	98	(42.8%)
PCI/CABG	75	(32.8%)
Heart failure	134	(58.5%)
Valvular heart disease	67	(29.3%)
TIA or stroke	33	(14.4%)
Ischaemic stroke	15	(6.6%)
Haemorrhagic stroke	1	(0.4%)
Prior ablation therapy	42	(18.3%)
History of ECV	123	(53.7%)
Medication prior to ECV:		
OAC:	227	(99.1%)
VKA	199	(86.9%)
Dabigatran	4	(1.7%)
Rivaroxaban	15	(6.6%)
Apixaban	9	(3.9%)
AAD:	138	(60.2%)
Amiodarone	55	(24.0%)
Sotalol	73	(31.9%)
Flecainide	14	(6.1%)
Rate control medication:		
Beta-blocker	118	(51.5%)
Verapamil	9	(3.9%)
Digoxin	33	(14.4%)

Legend of Table 1.

Shown are mean ± SD or n (%). ***COPD****=chronic obstructive pulmonary disease,* ***OSAS****= obstructive sleep apnea syndrome,* ***PCI****= percutaneous coronary intervention,* ***CABG****=coronary artery bypass grafting,* ***TIA****= transient ischemic attack,* ***OAC****= oral anticoagulation,* ***VKA****= vitamin K antagonist,* ***AAD*** *=anti-arrhythmic drug.*

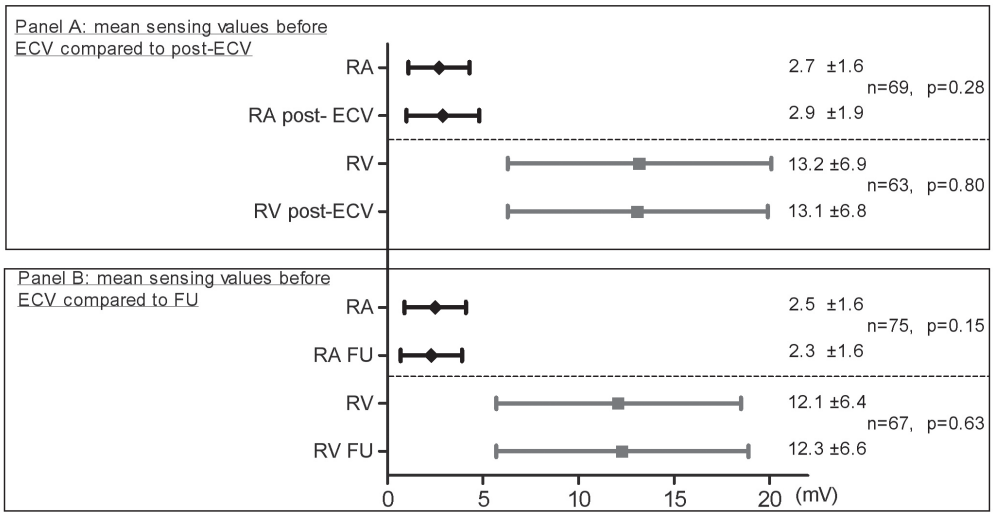

Figure 1. *Right atrial (RA) and right ventricular (RV) sensing values before ECV, immediately after ECV (post-ECV) and at follow up (FU) presented as mean (±SD).*

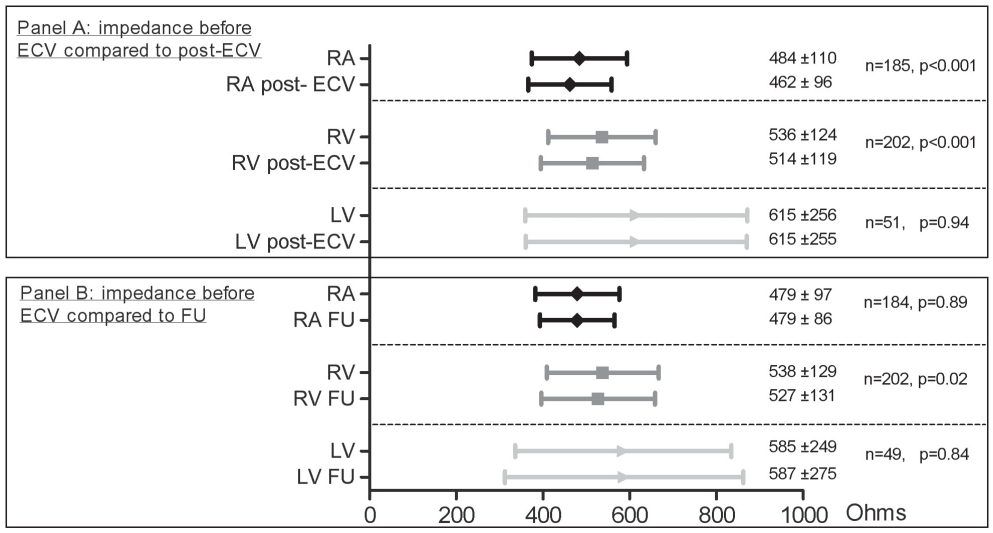

Figure 2. *Right atrial (RA), right ventricular (RV) and left ventricular (LV) impedance values before ECV, immediately after ECV (post-ECV) and at follow up (FU) presented as mean (±SD).*

Table 2. **Device and cardioversion parameters of patients with CIEDs undergoing ECV.**

Devices:		
PM	104	(45.4%)
ICD	69	(30.1%)
CRT	56	(24.5%)
Manufacturers:		
Boston Scientific	50	(21.8%)
Biotronik	37	(16.2%)
Medtronic	100	(43.7%)
St Jude Medical (now Abbott)	34	(14.8%)
Vitatron	6	(2.6%)
Cameron Health / Boston Scientific subcutaneous ICD	2	(0.9%)
Median duration in months from (last) device implantation till ECV	17.6	(IQR 5.5-41.1, range 0-157)
Arrhythmia:		
Atrial fibrillation	177	(77.3%)
Atrial flutter	48	(21.0%)
Atrial tachycardia	4	(1.7%)
Cumulative energy (J)	192	±108 range: 50-560J
Successful cardioversion	223	(97.4%)
First shock successful	185	(80.8%)
Number of shocks*:		
1 shock	188	(83.6%)
2 shocks	27	(12.0%)
3 shocks	10	(4.4%)
Paddle position†:		
Anteroposterior†	121	(85.8%)
Anterolateral†	17	(12.1%)
Internal (ICD) + anteroposterior†	3	(2.1%)

***PM**=pacemaker, **ICD**= implantable cardioverter defibrillator, **CRT**= cardiac resynchronization therapy, **IQR**= interquartile range.*
**based on n=225 due to missing data, † based on n=141 due to missing data.*

The results of device interrogation are presented in Figure 1-3. No significant differences between RA and RV sensing values before and immediately after ECV were observed (2.7mV±1.6 vs. 2.9mV±1.9, p=0.28 and 13.2mV±6.9 vs. 13.1mV±8.8, p=0.80 respectively). Similar results were observed for RA and RV sensing values before ECV and at follow up (mean follow-up 3±2 months; 2.5mV±1.6 vs. 2.3mV±1.6, p=0.15 and 12.1mV±6.4 vs. 12.3mV±6.6, p=0.63 respectively, Figure 1). A small yet significant decrease was observed in RA and RV impedance immediately after ECV (484±110 vs. 462±96 ohms, p<0.001 and 536±124 vs. 514±119 ohms, p<0.001 respectively), without clinical consequences. At follow up, RA impedance recovered, but although without clinical consequences, the acutely decreased mean RV impedance value after ECV did not recover to values before ECV (538±129 vs. 527±131 ohms, p=0.02; Figure 2). No significant changes in RA and RV threshold measurements were noted, Figure 3. Finally, no significant changes in LV lead threshold or impedance values were measured (Figure 2-3). Importantly, no CIED related complications or adverse events after external ECV were documented.

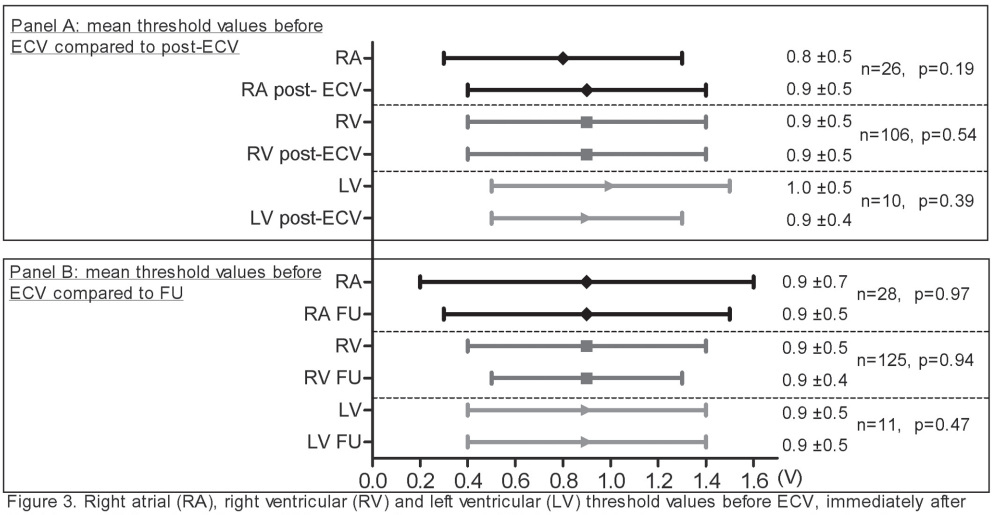

Figure 3. Right atrial (RA), right ventricular (RV) and left ventricular (LV) threshold values before ECV, immediately after ECV (post-ECV) and at follow up (FU) presented as mean (±SD). Threshold values at a constant pulse duration.

Figure 3. *RA, RV, and LV threshold values before ECV, immediately after ECV (post-ECV), and at FU presented as mean ± standard deviation. Threshold values at a constant pulse duration.* ***ECV*** *= electrical conversion;* ***FU*** *= follow-up;* ***LV*** *= left ventricular;* ***RA*** *= right atrial;* ***RV*** *= right ventricular.*

DISCUSSION

In this retrospective study no complications or CIED related adverse events were observed after external ECV in patients with different types of contemporary CIEDs. Immediate device interrogation after ECV revealed only a small but not clinically relevant decrease in RA and RV impedance. At follow-up, the RV impedance did not recover to the values before ECV, however, this was without clinical consequences. To the best of our knowledge, this is the largest study concerning the safety of external ECV in patients with contemporary CIEDs.

Data concerning the safety of external ECV in patients with CIEDs are scarce. A few case series have been published reporting device and/or lead dysfunction immediately after ECV [6-13], however, these case series were based on unipolar leads, anterolateral paddle position and monophasic shock waveforms. Because of the current use of biphasic shock waveforms, less energy is required for successful cardioversion which, in conjunction with an anteroposterior paddle position, reduces the risk of energy shunting to the leads which could lead to endocardial burns and fibrosis at the electro-myocardial interface [6,12]. This is confirmed by more recent reports showing no failure or abnormality of CIEDs after external ECV [12,14]. Manegold et al. prospectively compared the use of monophasic and biphasic shock waveforms in 44 patients with a pacemaker (29), ICD (12) or CRT (3). They reported a transient drop in lead impedance immediately after ECV, without clinical consequences. Although, biphasic shock waveforms required less energy for AF termination compared to monophasic shock waveforms, in both groups no device related complications or adverse events were reported[12]. However, as current ESC guidelines recommend the use of biphasic shock waveforms, only 23 patients included in that study represent current daily practice. Lüker et al, evaluated the safety of external ECV in 43 patients with biventricular devices, in this study an anteroposterior paddle position was preferred (87%) [14]. They found a significant elevation of LV lead threshold immediately after ECV and a trend towards a significant drop in impedance, both without clinical consequences. No serious adverse events were observed after ECV.

As described above and in accordance with previous reports, the present study showed a decrease in impedance immediately after ECV. A possible explanation for this could be by higher conductivity of the tissue due to ion shifting after ECV [12,14]. Most importantly, this finding had no clinical consequences.

ESC guidelines recommend an anteroposterior paddle position [15], however in this cohort, in 12.1% an anterolateral paddle position was used for unknown reason. Nevertheless, no complications, adverse events or remarkable changes were noted in those patients.

LIMITATIONS

Due to the retrospective observational design and due to effects of arrhythmias on measured parameters, complete data on device interrogation was not available in all patients, this could have influenced our results. However, the primary endpoint - complications and adverse events - was available in all included subjects. We did not assess other factors that could have possibly influenced our findings, for instance changes in the use of Class Ic anti-arrhythmic medication could have influenced the threshold values.

CONCLUSION

Our results suggest that external ECV can be performed safely in patients with contemporary CIEDS respecting the recommendations of the ESC guidelines to use biphasic shock waveforms and an anteroposterior paddle position. Immediate device interrogation seems unnecessary. Besides that it is redundant, it also causes unnecessary health care costs.

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IJC Heart & Vasculature 2021;36:100870.

Clinical utility of rhythm control by electrical cardioversion to assess the association between self-reported symptoms and rhythm status in patients with persistent atrial fibrillation

ABSTRACT

Background

The best strategy to assess the association between symptoms and rhythm status (symptom-rhythm correlation) in patients with atrial fibrillation (AF) remains unclear. We aimed to determine the clinical utility of rhythm control by electrical cardioversion (ECV) to assess symptom-rhythm correlation in patients with persistent AF.

Methods

We used ECV to examine symptom-rhythm correlation in 81 persistent AF patients. According to current clinical practice, the presence of self-reported symptoms before ECV and at the first outpatient clinic follow-up visit (within 1-month) was assessed to determine the prevalence of a symptom-rhythm correlation (defined as self-reported symptoms present during AF and absent in sinus rhythm or absent in AF and yet relief during sinus rhythm). In addition, we evaluated symptom patterns around ECV.

Results

Only in 18 patients (22%), a symptom-rhythm correlation could be documented. Twenty-eight patients (35%) did not show any symptom-rhythm correlation and 35 patients (43%) had an unevaluable symptom-rhythm correlation as these patients were in symptomatic AF both at baseline and at the first outpatient AF clinic follow-up visit. Importantly, self-reported symptom patterns around ECV were intra-individually variable in 10 patients (12%) without symptom-rhythm correlation (of which 9 patients (11%) had AF recurrence) and in 2 patients (2%) with an unevaluable symptom-rhythm correlation.

Conclusions

In patients with persistent AF, symptom assessment around rhythm control by ECV, once before ECV and once within 1-month follow-up, rarely identifies a symptom-rhythm correlation and often suggests changes in symptom pattern. Better strategies are needed to assess symptom-rhythm correlation in patients with persistent AF.

NTRODUCTION

Patient-tailored management of persistent atrial fibrillation (AF) relies on rate and/or rhythm control, antithrombotic treatment and management of concomitant cardiac diseases. [1] One of the main goals of AF rhythm control is amelioration of symptoms. Although a large proportion of patients with AF reports symptoms, [2] it often remains unclear whether all symptoms are related to AF or whether also other concomitant cardiovascular or non-cardiovascular conditions and risk factors contribute to overall symptom burden in an individual patient. Knowledge about the association between symptoms and rhythm status (symptom-rhythm correlation) has potential clinical implications as it may identify patients who profit from rhythm control in regard to reduction in symptom burden and improvement in quality of life. However, standardized strategies to assess symptom-rhythm correlation are currently not available. [3]

Electrical cardioversion (ECV) offers the opportunity to probe symptom-rhythm correlation. In patients in whom ECV is successful the time in sinus rhythm can be used to evaluate whether symptoms improve once sinus rhythm is restored (symptom-rhythm correlation), or whether symptom burden remains unaffected (no symptom-rhythm correlation). [4]

In this retrospective observational cohort study, we determined the clinical utility of rhythm control by ECV to assess symptom-rhythm correlation in patients with persistent AF. Therefore, in accordance with current clinical practice, we used self-reported symptom reports collected during the outpatient AF clinic visits before and after ECV to (1) examine the prevalence of a symptom-rhythm correlation (defined as self-reported symptoms present during AF and absent in sinus rhythm or absent in AF and yet relief during sinus rhythm), and (2) assess the symptom patterns around ECV in patients with persistent AF.

METHODS

Study design

This retrospective observational cohort study complies with the Declaration of Helsinki and was approved by the Institutional Review Board at the medical center (Committee reference number: NL 45118.068.13). Staff members of the independent Clinical Trial Center Maastricht performed the study monitoring and data management. All patients provided written informed consent.

Study population

Hemodynamic stable patients with persistent AF who underwent ECV in Maastricht University Medical Center (Maastricht, The Netherlands) were included in this study. Individuals were excluded if they were aged <18 years, were on antiarrhythmic drugs, previously underwent ablation therapy for AF or if the current episode of AF was classified as postoperative AF. Other exclusion criteria were the presence of a pacemaker unable to detect AF with a regular paced rhythm during AF, and a history of myocardial infarction within four weeks preceding recruitment into the study.

Data collection

Baseline clinical characteristics (demographics, concomitant cardiovascular conditions, and medication) were retrieved from patient medical records. Furthermore, we obtained the presence of self-reported symptoms and the predominant self-reported symptom type (symptom with highest self-reported symptom burden) of each individual patient before ECV and at the first outpatient AF clinic follow-up visit (within one month after ECV) from patient medical records. During structured history taking, the presence of the following symptoms and their symptom-specific burden before and after ECV were interrogated by the attending physician without using a validated tool: palpitations, dyspnea, reduced exercise tolerance, tiredness, chest pain, and others.

The presence of self-reported symptoms was determined to examine the prevalence of a symptom-rhythm correlation. Symptom-rhythm correlation was assessed by considering the association between self-reported symptoms and the rhythm status before and after ECV. Patients with symptoms prior to ECV and without symptoms in sinus rhythm as well as asymptomatic patients before ECV with yet symptom relief during sinus rhythm were defined as symptom-rhythm correlation. In persistent AF patients who perceived themselves as asymptomatic before ECV, ECV was performed to see if restoration and maintenance of sinus rhythm can 'unmask' a previously suppressed level of symptoms. The symptom-rhythm correlation was absent in patients with symptoms before ECV who remained symptomatic during sinus rhythm (regardless of changes in predominant symptom type) or in patients with symptoms prior to ECV and without symptoms in AF after ECV. Asymptomatic patients before ECV with or without symptoms in AF or sinus rhythm afterwards had no symptom-rhythm correlation as well. The symptom-rhythm correlation was unevaluable in patients who were symptomatic in AF before ECV and at the first outpatient AF clinic follow-up visit.

The predominant self-reported symptoms before and after ECV were collected to assess the symptom patterns around ECV. Intra-individually variable symptom patterns were defined as changes in predominant self-reported symptoms within patients around ECV.

Statistical analysis

All statistical analyses were performed using IBM SPSS 25.0 software (SPSS, Inc., Chicago, USA) and statistical significance was assumed at a 5% level. Histograms and Shapiro-Wilk tests were used to check for normality. Categorical variables were represented as numbers of patients (n) with percentages. Normally distributed continuous variables were reported as mean ±standard deviation (SD) and non-normal distributed continuous variables were presented as median with interquartile range (IQR). For the comparison of categorical data, the Pearson's chi-squared tests or alternatively Fisher's exact tests were used, as appropriate. Differences in continuous parameters were compared using one-way ANOVA and Kruskal-Wallis.

RESULTS

Patients

A total of 81 patients were included in this analysis. The median age was 70 years (IQR, 64-75) and 19 patients (23%) were female. There were 51 patients (63%) with a first documented episode of AF and in 38 patients (47%) the current AF episode duration was ≤3 months (*Table 1*). Of all 81 persistent AF patients who underwent ECV, 63 were symptomatic (78%). ECV was performed in 18 additional persistent AF patients (22%) who perceived themselves as asymptomatic before ECV to see if restoration and maintenance of sinus rhythm can 'unmask' a previously suppressed level of symptoms. ECV was successful in 76 patients (94%), unsuccessful in 3 patients (4%), and 2 patients (2%) had immediate recurrence of AF (IRAF). Within one month after ECV, 52 patients (64%) had a documented recurrence of AF.

Symptom-rhythm correlation

The minority of patients (18 patients, 22%) displayed a symptom-rhythm correlation of which 17 (21%) had symptoms prior to ECV and no symptoms in sinus rhythm and 1 (1%) was asymptomatic before ECV with yet symptom relief during sinus rhythm (in this patient, ECV 'unmasked' a previously suppressed level of symptoms) (*Figure 1, panel a; Figure 2, panel a*). Twenty-eight patients (35%) did not show any symptom-rhythm correlation (*Figure 1, panel b; Figure 2, panel a and b)* and 35 patients (43%) with relapse of AF had an unevaluable symptom-rhythm correlation as these patients were in

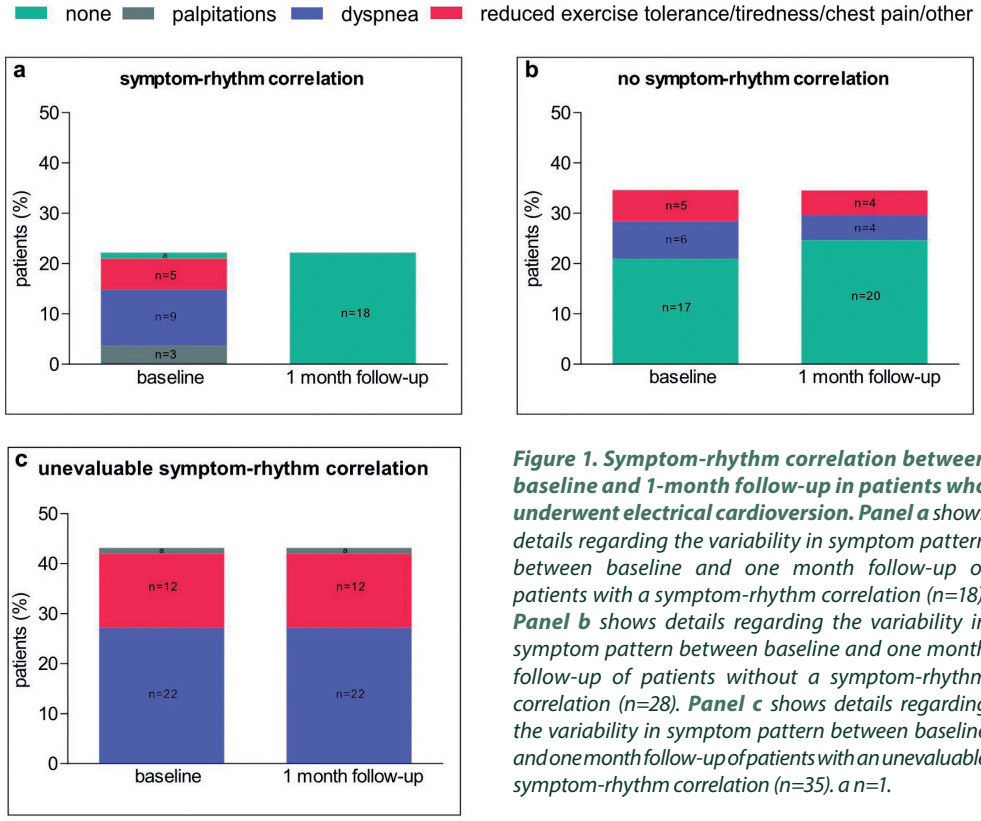

Figure 1. Symptom-rhythm correlation between baseline and 1-month follow-up in patients who underwent electrical cardioversion. Panel a *shows details regarding the variability in symptom pattern between baseline and one month follow-up of patients with a symptom-rhythm correlation (n=18).* ***Panel b*** *shows details regarding the variability in symptom pattern between baseline and one month follow-up of patients without a symptom-rhythm correlation (n=28).* ***Panel c*** *shows details regarding the variability in symptom pattern between baseline and one month follow-up of patients with an unevaluable symptom-rhythm correlation (n=35). a n=1.*

symptomatic AF both at baseline and at the first outpatient clinic visit (*Figure 1, panel c; Figure 2 panel b*). Baseline clinical characteristics of patients with and without symptom-rhythm correlation and of patients with an unevaluable symptom-rhythm correlation are reported in *Table 1*. All patient characteristics were comparable. The findings hold true when we excluded patients with prior attempts of rhythm control (previous ECV or antiarrhythmic medication therapy) because of potential 'treatment expectation bias' (supplementary material online, *Table S1*).

Predominant self-reported symptoms

Before ECV, dyspnea was the most common symptom (n=37, 46%), followed by reduced exercise tolerance (n=16, 20%), tiredness (n=5, 6%), palpitations (n=4, 5%) and chest pain (n=1, 1%). Twenty-two percent of patients (n=18) reported no symptoms. Of the 29 patients with sinus rhythm after ECV, 24 (83%) were asymptomatic, 3 (10%) had reduced exercise tolerance and 2 (7%) had dyspnea at 1-month follow-up (*Figure 3, panel a-d*). In the 52 patients with a recurrence of AF after ECV, there were 14 patients (27%) without symptoms, 24 (46%) with dyspnea, 8 (15%) with reduced exercise tolerance, 3 (6%) with tiredness, 1 (2%) with palpitations, 1 (2%) with chest pain and 1 (2%) with other symptoms at one month (*Figure 3, panel a-d*). Importantly, self-reported symptom patterns around ECV were intra-individually variable in 10 patients (12%) without symptom-rhythm correlation (of which 9 patients (11%) had AF recurrence) and in 2 patients (2%) with an unevaluable symptom-rhythm correlation (*Figure 2, panel a and b).*

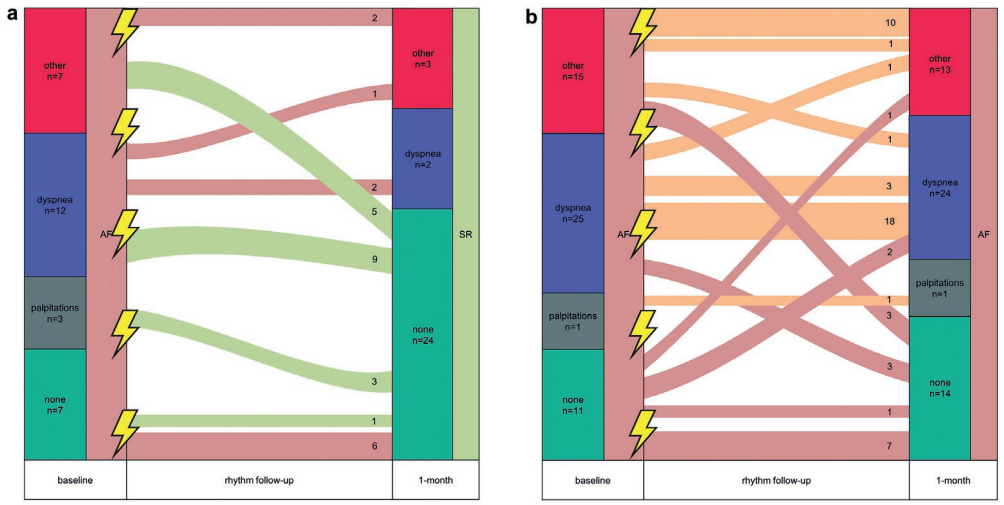

Figure 2. Symptom variability around electrical cardioversion per patient. *Shown is the symptom variability around electrical cardioversion (ECV) among patients without recurrence of atrial fibrillation (AF)* ***(panel a)*** *and with recurrence of AF* ***(panel b)****. Other includes the following symptoms: reduced exercise tolerance, tiredness, chest pain, and others. The green lines indicate patients with a symptom-rhythm correlation around ECV (defined as self-reported symptoms present during AF and absent in sinus rhythm (SR) or absent in AF and yet relief during sinus rhythm). The red lines indicate patients without a symptom-rhythm correlation around ECV. The orange lines indicate patients with an unevaluable symptom-rhythm correlation around ECV. The lightning symbols are used to display the moment of ECV.*

DISCUSSION

In this retrospective cohort study, the minority of patients showed a symptom-rhythm correlation (defined as predominant self-reported symptoms present during AF and absent in sinus rhythm or absent in AF and relief during sinus rhythm) around ECV. We found a high variability in self-reported symptoms before and after ECV in patients with AF recurrence.

Symptom-rhythm correlation and symptom pattern around electrical cardioversion

The low prevalence of symptom-rhythm correlation and the high remaining symptom burden after rhythm control by ECV do not support prior work showing that the majority of patients who were symptomatic in AF before ablation became asymptomatic in sinus rhythm after ablation.[5, 6] Additionally, patients with a successful ablation had greater reduction in symptoms compared to patients with an unsuccessful ablation. [7, 8] An explanation might be a different symptom perception in patients with paroxysmal and persistent AF, however invasive interventions per se may also lead to alterations in perception of AF caused by a placebo effect. [8-10] Moreover, patients' limited prior knowledge of AF, previous health experiences and interactions with health care providers may influence symptom perception as well. [11] In general, blinded sham-controlled studies may be needed to definitely rule out a placebo effect of rhythm-control, particularly if symptom-burden is one of the main outcome-measures.

The main goal of rhythm control strategies is amelioration of symptoms in AF patients. In regard to symptom control, the best responder to rhythm control (by pharmacological interventions, ECV or AF-ablation procedures) would be an AF patient who is predominantly symptomatic

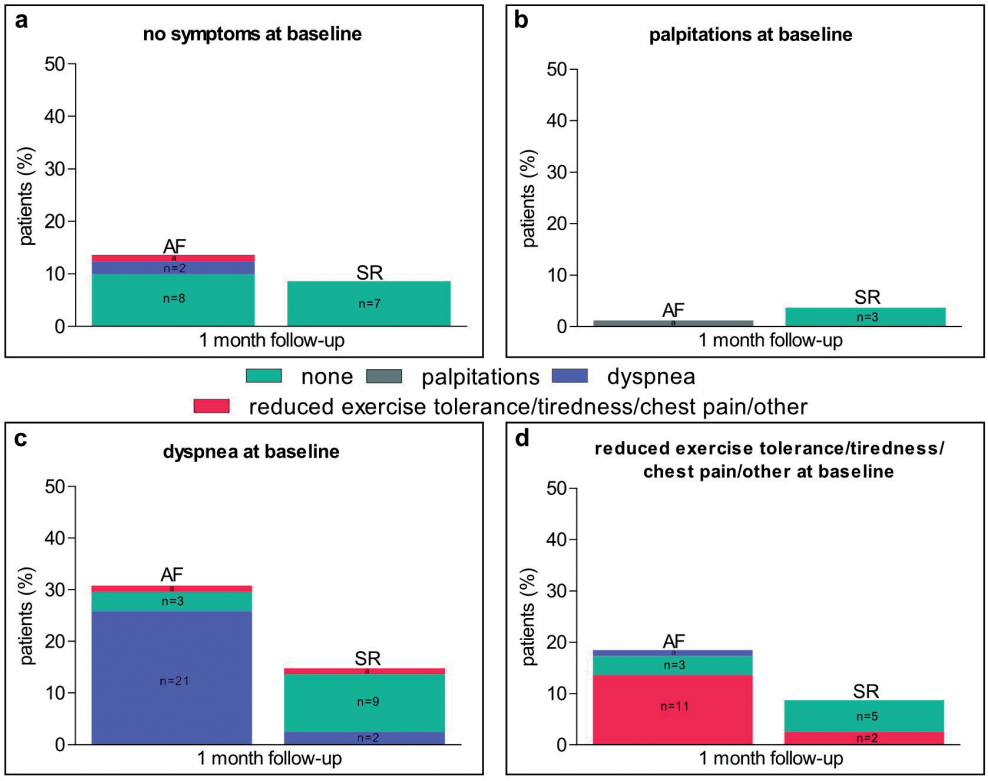

Figure 3. Symptom pattern before and after electrical cardioversion. *Shown is the symptom pattern between symptoms at baseline and symptoms at one month follow-up among 81 patients with and without recurrence of atrial fibrillation (AF).* ***Panel a-d*** *shows the percentage of patients with a specified baseline symptom and their symptoms at 1-month follow-up. a n=1. SR, sinus rhythm.*

because of AF-related symptoms. Furthermore, severe symptomatic patients would have a higher likelihood of symptom improvement after the achievement of sinus rhythm compared to minimally symptomatic or asymptomatic patients. [10] Therefore, the assessment of the underlying pathophysiological condition mainly contributing to symptoms is important to guide the decision for rhythm versus rate control. Theoretically, in symptomatic patients without symptom-rhythm correlation, non-AF related factors such as cardiovascular or non-cardiovascular conditions and risk factors, which do not change after successful rhythm control, are likely contributing to overall symptom burden in an individual patient. However, in our study, the cardiovascular conditions and risk factors of patients with and without symptom-rhythm correlation as well as of patients with an unevaluable symptom-rhythm correlation were quite similar. Importantly, in addition to the amelioration of symptoms, recent studies also showed that rhythm control (AF ablation therapy and treatment with antiarrhythmic drugs) may also be associated with a reduction in cardiovascular outcomes, potentially even irrespective of improvement of symptoms and in asymptomatic patients. [12-14] Therefore, the role of systematic symptom-rhythm correlation assessment using ECV as a diagnostic tool to guide decision on rhythm control in patients with persistent AF needs to be investigated in future studies.[10, 15]

Table 1. **Baseline characteristics of the patients with, without and with unevaluable symptom-rhythm correlation.**

	Total (n=81)	Symptom-rhythm correlation Yes (n=18)	No (n=28)	Unevaluable (n=35)	P-value
Demographics					
Female	19 (23)	7 (39)	8 (29)	4 (11)	0.06
Age (years), median (IQR)	70 (64-75)	69 (61-76)	71 (64-75)	70 (67-75)	0.71
Body mass index (kg/m^2), mean ±SD, (n=80) [b]	29.2±4.6	28.5±5.7	29.4±3.9	29.4±4.7	0.74
First detected atrial fibrillation[b]	51/77 (66)	10/18 (56)	19/27 (70)	22/32 (69)	0.55
Duration current atrial fibrillation episode ≤3 months[b]	38/79 (48)	8/18 (44)	12/27 (44)	18/34 (53)	0.76
Previous electrical cardioversion	13 (16)	4 (22)	3 (11)	6 (17)	0.59
Previous antiarrhythmic medication	5 (6)	2 (11)	0 (0)	3 (9)	0.22
Concomitant cardiovascular conditions					
CHA_2DS_2-VASc score ≥2[c]	65 (80)	13 (72)	23 (82)	29 (83)	0.62
Arterial hypertension	48 (59)	11 (61)	20 (71)	17 (49)	0.18
Stroke	7 (9)	1 (6)	3 (11)	3 (9)	1.00
Transient ischemic attack	8 (10)	0 (0)	2 (7)	6 (17)	0.15
Heart failure[b d]	17/75 (23)	5/17 (29)	6/25 (24)	6/33 (18)	0.66
Obstructive sleep apnea syndrome	9 (11)	1 (6)	4 (14)	4 (11)	0.82
Medication					
Renin-angiotensin antagonists	42 (52)	12 (67)	14 (50)	16 (46)	0.34
Aldosterone antagonists	5 (6)	0 (0)	3 (11)	2 (6)	0.36
Anticoagulants	81 (100)	18 (100)	28 (100)	35 (100)	
Antiplatelets	5 (6)	2 (11)	1 (4)	2 (6)	0.71
Beta-blockers	69 (85)	17 (94)	26 (93)	26 (74)	0.07
Calcium channel blockers	17 (21)	3 (17)	7 (25)	7 (20)	0.78
Dihydropyridine[b]	13/17 (76)	2/3 (67)	7/7 (100)	4/7 (57)	0.18
Diuretics	31 (38)	7 (39)	10 (36)	14 (40)	0.94

Percentages may not total 100 because of rounding. [a] *Values depicted as number of patients (n) with percentages unless indicated otherwise.* [b] *Number of patients with available information is given since some patients had missing values.* [c] *The CHA_2DS_2-VASc score is a well-established tool used for risk stratification of stroke in patients with atrial fibrillation, with scores ranging from 0 to 9 and a higher score corresponds to a greater risk. Congestive heart failure, hypertension, diabetes, vascular disease, an age of 65 years to 74 years and female gender are each allocated one point, and an age of more than 75 years and previous stroke or transient ischemic attack are each allocated two points.*[1] [d] *Heart failure was defined as a left ventricular ejection fraction of less than 40%.* [e] *SD, standard deviation; IQR, interquartile range.*

The assessment of symptom-rhythm correlation has potential clinical implications as it may identify patients likely profiting from rhythm control strategies to improve their symptom burden and quality of life. However, identifying a symptom-rhythm correlation in AF patients is challenging. The best way to determine symptom-rhythm correlation remains unclear. The high recurrence rate of AF within the first month is significantly limiting the diagnostic utility of ECV at one month. To enhance the performance of symptom-rhythm correlation assessment, the period in sinus rhythm after ECV may be lengthened by specific patient selection (e.g. smaller left atrial size)[16] or using temporary amiodarone or flecainide, which, however as such may affect symptom burden.[4] Besides, as it is established that ECV is associated with a 24-hour relapse gap of AF recurrence,[17] symptom assessment at 24 hours may give sufficient opportunity for an effective evaluation of changes in symptoms around ECV. Additionally, symptom burden was interrogated once at baseline and once at one month follow-up after ECV (in accordance with current clinical practice). A more longitudinal assessment of symptoms during simultaneous rhythm monitoring in persistent AF patients undergoing ECV may provide a more accurate approach to assess a symptom-rhythm correlation and to distinguish between AF-related symptoms (AF-symptoms) and unspecific disease-related symptoms (symptoms in AF). A better characterization and a better understanding of the mechanisms of symptoms in AF patients and symptom burden may help to obtain the correct diagnosis, chose an appropriate treatment (rhythm control vs. rate control), and assess the actual result of a treatment. Additionally, the absence of a clear symptom-rhythm correlation may provide a plausible basis for a structured assessment and then for targeted and comprehensive management of co-morbidities contributing to symptom burden.

There was a high variability in self-reported symptoms before and after ECV in patients with AF recurrence. This heterogeneity in terms of symptom presentation suggests that symptoms in patients with AF may be the manifestation of multiple pathophysiologic mechanistic pathways.[3] Patients with first-detected AF are more symptomatic than patients with a longer history of AF[18] and even in highly symptomatic AF patients, asymptomatic episodes may occur. [9] Moreover, there are higher rates of atypical symptoms in elderly with AF. [19] Although most AF patients experience symptoms during AF episodes, [2, 20] symptom perception is highly variable. [1, 9] Sociodemographic- and sex-specific factors as well as anxiety- and depression-related mechanisms may be involved in the type or severity of self-reported symptoms in AF patients. [21] Additionally, symptoms in AF patients related to certain comorbidities such as heart failure, obesity, diabetes, coronary artery disease, arterial stiffness, and sleep-disordered breathing may perpetuate and contribute significantly to the perception and judgement of the frequency and severity of AF-related symptoms as well. [22-25] Therefore, additional studies evaluating the effect of specific concomitant non-cardiovascular and cardiovascular conditions and risk factors on overall symptom burden are needed.

Limitations

Several limitations of our study should be mentioned. First, the sample size of our study was relatively small and there may be selection bias, as we included only those patients who were not on antiarrhythmic drugs. Therefore, there should be caution in generalizing our findings to all patients with persistent AF, as results may differ in other patient populations. Second, the presence of symptoms and if present, the predominant self-reported symptoms around ECV were obtained retrospectively from patient medical records (in accordance with current clinical practice). Thus, there is a risk that the coverage of different symptoms is not as complete as in a questionnaire, diary or structured interview. Third, we just applied one technique to assess symptom-rhythm correlation, namely assessment of symptoms once before ECV and once at one month after ECV (spot-check symptom assessment). A more longitudinal assessment of symptoms during simultaneous rhythm

monitoring around ECV may provide a more accurate approach to assess a symptom-rhythm correlation. Further studies are required to test the utility of such approach. Fourth, we presented symptom-rhythm correlation as a categorical variable (yes or no). But probably, symptom-rhythm correlation assessment is not that "black or white", as also other concomitant cardiovascular or non-cardiovascular conditions and risk factors may contribute to overall symptom burden. A point to take also into account is that prior work suggested that the physician's assessment of AF-specific symptoms is an underestimation of patients AF-specific symptoms, especially when they are mild, which may affect the variability in symptoms and thus the prevalence of symptom-rhythm correlation around ECV

CONCLUSIONS

In patients with persistent AF, spot-check-based symptom-rhythm correlation assessment around rhythm control by ECV, once before ECV and once at the first outpatient AF clinic follow-up visit (within one month after ECV), rarely identifies a symptom-rhythm correlation. Additionally, ECV often suggests changes in symptom pattern. Further research is warranted to identify more optimal strategies to assess symptom-rhythm correlation in patients with persistent AF and to establish the clinical implications of symptom-rhythm correlation assessment for AF management.

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SUPPLEMENTARY FILE

Table S1. **Baseline characteristics of the patients without prior attempts of rhythm control.**

	Total (n=65)	Symptom-rhythm correlation: Yes (n=13)	No (n=25)	Unevaluable (n=27)	P-value
Demographics					
Female	15 (23)	5 (39)	7 (28)	3 (11)	0.12
Age (years), median (IQR)	70 (64-75)	69 (59-75)	70 (64-75)	70 (66-74)	0.77
Body mass index (kg/m^2), median (IQR)	29.05 (25.10-32.15)	29.03 (23.04-34.87)	29.35 (26.72-31.77)	28.68 (24.93-32.11)	0.85
First detected atrial fibrillation[b]	50/62 (81)	9/13 (69)	19/24 (79)	22/25 (88)	0.35
Duration current atrial fibrillation episode ≤3 months[b]	31/63 (49)	6/13 (46)	11/24 (46)	14/26 (54)	0.83
Concomitant cardiovascular conditions					
CHA_2DS_2-VASc score ≥2[c]	52 (80)	9 (69)	20 (80)	23 (85)	0.50
Arterial hypertension	40 (62)	8 (62)	19 (76)	13 (48)	0.12
Stroke	6 (9)	0 (0)	3 (12)	3 (11)	0.64
Transient ischemic attack	6 (9)	0 (0)	1 (4)	5 (19)	0.13
Heart failure [b d]	15/61 (25)	4/13 (31)	5/22 (23)	6/26 (23)	0.84
Obstructive sleep apnea syndrome	7 (11)	1 (8)	4 (16)	2 (7)	0.59
Medication					
Renin-angiotensin antagonists	34 (52)	9 (69)	12 (48)	13 (48)	0.39
Aldosterone antagonists	4 (6)	0 (0)	3 (12)	1 (4)	0.41
Anticoagulants	65 (100)	13 (100)	25 (100)	27 (100)	
Antiplatelets	5 (8)	2 (15)	1 (4)	2 (7)	0.42
Beta-blockers	56 (86)	13 (100)	23 (92)	20 (74)	0.05
Calcium channel blockers	13 (20)	1 (8)	6 (24)	6 (22)	0.46
Dihydropyridine[b]	11/13 (85)	1/1 (100)	6/6 (100)	4/6 (67)	0.54
Diuretics	27 (42)	5 (39)	10 (40)	12 (44)	0.92

Percentages may not total 100 because of rounding. [a] Values depicted as number of patients (n) with percentages unless indicated otherwise. [b] Number of patients with available information is given since some patients had missing values.[c] The CHA_2DS_2-VASc score is a well-established tool used for risk stratification of stroke in patients with atrial fibrillation, with scores ranging from 0 to 9 and a higher score corresponds to a greater risk. Congestive heart failure, hypertension, diabetes, vascular disease, an age of 65 years to 74 years and female gender are each allocated one point, and an age of more than 75 years and previous stroke or transient ischemic attack are each allocated two points.[1] [d] Heart failure was defined as a left ventricular ejection fraction of less than 40%. [e] IQR, interquartile range.

PART IV

Perspectives in cardioversion for AF

N.A.H.A. Pluymaekers, A.N.L. Hermans, R.M.J. van der Velden, D.W. den Uijl, B. Vorstermans, S. Buskes, J.M. Hendriks, K. Vernooy, H.J.G.M. Crijns, D. Linz.

Int J Cardiol Heart Vasc. 2020 May 8;28:100533.

On-demand app-based rate and rhythm monitoring to manage atrial fibrillation through teleconsultations during COVID-19

RESEARCH LETTER

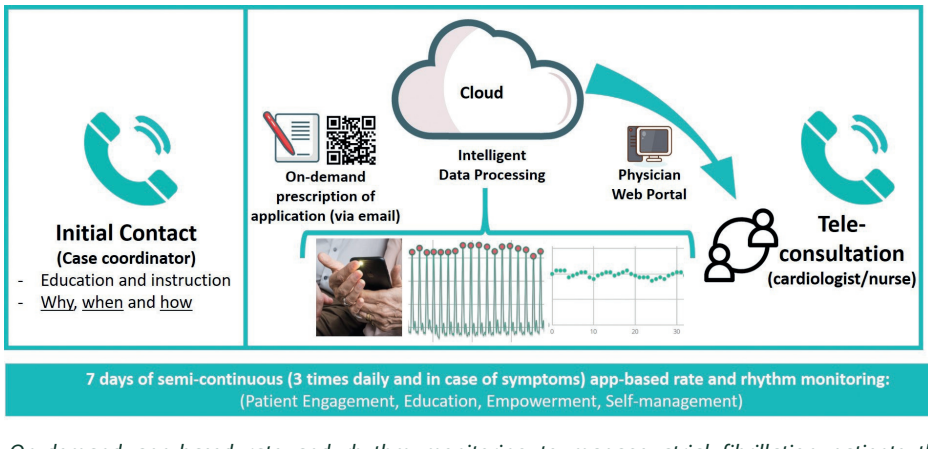
During the coronavirus 2019 (COVID-19) pandemic, one important contribution to keep the number of cases at a manageable level for the medical system (flattening the curve) was social distancing measures and, in particular, keeping vulnerable multimorbid patients with chronic conditions, such as atrial fibrillation (AF), out of the hospital. Consequently, from one day to another, traditional face-to-face outpatient consultations were transformed into tele-consultations. Initially, as no infrastructure was readily available to remotely assess vital measures, tele-consultations were conducted without any information about heart rhythm or rate of the patients. Adaptation of medication was mainly based on physician´s instinct and patient-reported symptoms rather than on objective measures. Herein, we describe how we implemented a remote on-demand monitoring infrastructure, which was based on a mobile phone app using photoplethysmography (PPG) technology allowing rate and rhythm monitoring around tele-consultations (summarized in the **figure**).

We asked our secretaries, who were working from home, to call all patients 5-7 days before scheduled tele-consultations. The patients were instructed to download the FibriCheck mobile phone app (www.fibricheck.com). This app is CE marked, connected to a secured and certified cloud and validated (sensitivity: 96%; specificity: 97%) to detect AF via PPG signals and to provide heart rate measures during sinus rhythm and AF[1,2]. A manual outlining the download and registration process of the app was sent to the patient via email. After download and registration, patients activated a 7-day on-demand prescription by scanning a QR code which linked the app to a cloud accessible by the treating physician. The patients were instructed to use the app three times per day and in the case of symptoms. All patients agreed on anonymous use of the collected data in the cloud.

Between March 25 and April 1 2020, 38 consecutive patients with a planned tele-consultation for AF management in the Maastricht University Medical Centre+ were contacted (age 66 years (range 40-78), 57% female). Thirty (79%) patients agreed to use the app, six (16%) patients did not have access to a mobile phone or tablet and were therefore excluded, two (1%) patients refused to use the app. During the tele-consultation at 5-7 days after the initial patient contact, the patients´ feedback was overwhelmingly positive. In total, 651 measurements were recorded and the quality of just 64 (10%) measurements evenly distributed across the population was too low for automatic analysis. The FibriCheck algorithm defined 398 (61%) measurements as normal sinus rhythm, 143 (22%) as AF and 46 (7%) as sinus rhythm with extrasystoles. The average number of measurements per participant was 22. After each measurement, symptoms were assessed by the app: 77% of measurements were asymptomatic, dyspnea was present in 5%, palpitations in 2%, chest pain in 1% and in 15% other symptoms were reported. FibriCheck information was used for management of rate and rhythm control medication in patients planned for AF outpatient clinic or follow-up after AF ablation.

During COVID-19, we implemented an on-demand app-based rate and rhythm monitoring to manage AF patients through tele-consultations in our AF-clinic. Several key elements are important during the implementation of the described mobile health (mHealth) infrastructure. A case coordinator, in our team the secretary, is the main contact person for the patients explaining the app or in case of issues[3]. Patient engagement and education are important aspects of this intervention[4]. Clear instructions are required concerning why, how, and when to use the app. Patients were made aware of their critical role in this process and the importance of the measurements for treatment decisions. Active engagement and empowerment to undertake this self-management intervention contributed to regular use of the app.

mHealth has been shown to play an important role in screening and management of AF[5]. This application of mHealth is new compared to previous settings. The goal was to monitor rate and rhythm remotely just around tele-consultations to provide basic vital parameters to allow a better



On-demand app-based rate and rhythm monitoring to manage atrial fibrillation patients through tele-consultation.

assessment of the disease state of the patient and to support in treatment decisions. This on-demand approach was regulated by a prescription to use the app for a limited predefined time period, which avoids unnecessary data-load and additional follow-up patients-contacts.

The relatively low cost, convenience, and broad accessibility of the mobile phone app used in this approach may allow a fast and broad implementation of the herein described mHealth infrastructure during the COVID-19 pandemic. No hardware is required which has several hygienic and logistical advantages. A potential disadvantage is, that no electrocardiogram can be provided, but the algorithm used by the app can validly inform about the presence of AF and current heart rate.

In conclusion, we have demonstrated, that it is feasible to implement a novel app-based on-demand rhythm and rate monitoring infrastructure to safely and efficiently provide tele-consultations in an AF population during the COVID-19 pandemic. Finally, further research and reimbursement solutions are required to allow long-term implementation of this infrastructure in the management of AF patients through tele-consultations in the future.

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N.A.H.A. Pluymaekers, A.N.L. Hermans, R.M.J. van der Velden, M. Gawałko, D.W. den Uijl, S. Buskes, K. Vernooy, H.J.G.M. Crijns, J.M. Hendriks,* D. Linz*.

*Shared last authorship

Europace 2021;23:345-52.

Implementation of an on-demand app-based heart rate and rhythm monitoring infrastructure for the management of atrial fibrillation through teleconsultation: TeleCheck-AF

ABSTRACT

During the coronavirus 2019 (COVID-19) pandemic, outpatient visits in the atrial fibrillation (AF) clinic of the Maastricht University Medical Centre (MUMC+) were transferred into teleconsultations. However, data on heart rate and rhythm was not available and hindered appropriated management of AF. In line with the fundamental aspects of integrated care, including actively involving patients in the care process and providing comprehensive care by a multidisciplinary team, we implemented a mobile health (mHealth) intervention to support teleconsultations with AF patients: TeleCheck-AF. The TeleCheck-AF approach guarantees the continuity of comprehensive AF management and supports integrated care through teleconsultation during COVID-19. It incorporates three important components: (1) a structured teleconsultation ("Tele"), (2) a CE-marked app-based on-demand heart rate and rhythm monitoring infrastructure ("Check") and (3) comprehensive AF management ("AF"). In this manuscript we describe the components and implementation of the TeleCheck-AF approach in an integrated and specialised AF-clinic through teleconsultation. The TeleCheck-AF approach is currently implemented in numerous European centers during COVID-19.

Keywords
Teleconsultation, mHealth, telehealth, atrial fibrillation, integrated care, mobile app.

What's New

- On-demand heart rate and rhythm monitoring infrastructures support integrated care through teleconsultation.
- TeleCheck-AF guarantees the continuity of comprehensive AF management through teleconsultation during COVID-19.
- The TeleCheck-AF approach is currently implemented in numerous European centers during COVID-19.

BACKGROUND

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia and associated with morbidity such as heart failure and an increased risk of thromboembolic complications, and mortality.[1] Patients with AF are considered vulnerable and monitoring of vital parameters, particularly heart rhythm and rate, is important and recommended to guide treatment decisions and prevent AF-related morbidity, such as tachy-cardiomyopathy.[2]

During the coronavirus 2019 (COVID-19) pandemic, social distancing was implemented as part of the strategy to prevent extensive spread of the virus and consequently keeping the number of cases at a manageable level for the medical system (flattening the curve). Despite these preventive interventions, as of 3 June 2020, 6 348 900 confirmed cases of severe acute respiratory syndrome virus 2 (SARS-CoV-2) infections causing COVID-19 have been reported globally, including 380 810 deaths.[3] Among these, a significant proportion of affected individuals appears to suffer from concomitant cardiovascular conditions.[4] Medical centers responded by keeping vulnerable multi-morbid patients with chronic conditions out of the hospital and elective cases as well as outpatient appointments were cancelled or performed as teleconsultations, where possible.

Early during the COVID-19 pandemic, the AF outpatient clinic (AF-clinic) of the Maastricht University Medical Centre (MUMC+) was restructured to maintain the management of vulnerable multimorbid AF patients out of the hospital to prevent worsening of the condition as well as to prevent AF-related hospitalisations. Traditional face-to-face outpatient consultations in AF-clinics were transferred into teleconsultations. The downside of this was that teleconsultations were conducted without any information about heart rhythm or rate of the patients, which resulted in discomfort and uncertainty of the physician and patient. While symptoms could be assessed by detailed history taking, the presence of AF, and even more important, the ventricular rate during AF in patients with persistent AF prone to develop tachy-cardiomyopathy was not known. Adoption of medication was mainly based on physician´s instinct and subjective patient-reported symptoms rather than on objective measures, and hindered a safe and individualized treatment approach, which is one of the goals of integrated AF-clinics.

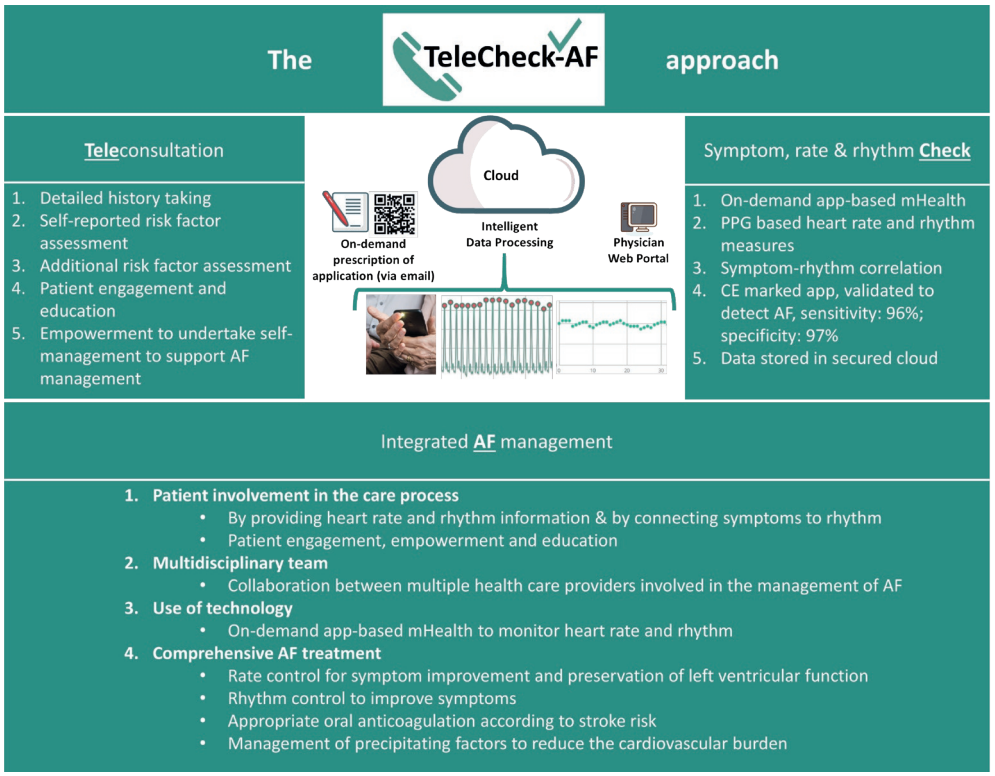
In line with the fundamental aspects of integrated care, such as actively involving patients in the care process and providing comprehensive care by a multidisciplinary team, we implemented a mobile health (mHealth) intervention to support teleconsultations with AF patients: TeleCheck-AF. In this manuscript we describe the components and implementation of the TeleCheck-AF approach in an integrated and specialised AF-clinic through teleconsultation during COVID-19.

THE TELECHECK-AF APPROACH

The TeleCheck-AF approach guarantees the continuity of comprehensive AF management and supports integrated care through teleconsultation during COVID-19. It incorporates three important components: (1) a structured teleconsultation ("Tele"), (2) an app-based on-demand heart rate and rhythm monitoring infrastructure ("Check") and (3) comprehensive AF management ("AF") (**Central Figure**).

1) TELEconsultation

Teleconsultation allows healthcare professionals to conduct remote patient consultations and communication between physicians.[5] It can be organized by a telephone conversation as well as by videoconferencing or videotelephony. Cardiologists/electrophysiologists as well as specialized AF nurses can be involved in teleconsultation and all contribute to patient education and ultimately in shared decision-making processes. According to current AF guidelines,[2] patient characteristics, comorbidities and AF risk factors should be assessed, and as such structured history taking is an



Figuur 1. Central Figure. *The TeleCheck-AF approach consist of three important components. A structured teleconsultation ("Tele"), an app-based on-demand heart rate and rhythm monitoring infrastructure ("Check") and a comprehensive atrial fibrillation management ("AF").*

important part of the teleconsultation. Although new teleconsultation solutions can produce remote situations that are relatively similar to face-to-face interactions, a standardized assessment of heart rate and rhythm remains challenging. In TeleCheck-AF, we introduce an on-demand app-based heart rate and rhythm monitoring infrastructure for the integration of remote documentation and guidance of AF management through teleconsultation.

2) On-demand app-based symptom, heart rate and rhythm CHECK

Remote heart rate and rhythm assessment in TeleCheck-AF is ensured by an on-demand monitoring infrastructure, which is based on a mobile phone app (FibriCheck®) using photoplethysmography (PPG) technology through the built-in camera. This app is CE marked, connected to a secured and certified cloud and validated (sensitivity: 96%; specificity: 97%) to detect AF via PPG signals and to provide rate measures during sinus rhythm and AF.[6,7] Patients are instructed to use this app 3 times every day and in case of symptoms to provide a semi-continuous longitudinal information about heart rate, rhythm and symptoms. The simultaneous assessment of heart rhythm and symptoms in the app allows assessment of symptom-rhythm correlation. The goal is to provide heart rate and rhythm information to allow a better assessment of the disease state of the patient and to support in treatment decisions during the teleconsultation. On-demand, the app can be activated for a limited predefined time period by a QR-code, which acts as a mHealth-prescription. Once the app

is activated by the QR-code, all PPG recordings are instantly submitted to a secured cloud which is accessible by the treating physician and can be used during the teleconsultation. In this TeleCheck-AF approach we propose activation of the app for 7 days. However, dependent on the clinical question and the physician preference, the use of the app can be adapted and controlled by providing respective QR-codes. The app regularly reminds the patients by pop-up messages to assess heart rate and rhythm which supports adherence and provides suggestions on how to improve recording quality in case of failed measurements. Additionally, the app provides educational information about AF, its complications and treatment.

3) AF management

The management of AF consists of four main domains: i) rate control for symptom management and preservation of left ventricular function, ii) rhythm control to improve symptoms, iii) prescribing appropriate oral anticoagulation according to stroke risk to prevent thromboembolic complications, and iv) management of precipitating factors (i.e. underlying cardiovascular conditions and modifiable risk factors) to reduce the cardiovascular burden.[2] Given the multifaceted character of AF management and limitations due to fragmentation of care, novel models of care delivery have been identified to improve efficiency and coordination of care, whilst improving clinical and patient outcomes. Integrated care is such an approach that is based on the principles of the Chronic Care Model[8] and aims to provide care which is in line with the patient's needs, preferences and values, and is based on the best available evidence. The concept of integrated care for AF management consists of four fundamental and indispensable aspects, including:

Patient involvement in the care process: Following a patient centered approach, it is important to actively involve patients and their caregivers in the care delivery, which includes involvement in decision making as well as undertaking self-management activities to support the treatment.[9] Engagement is an important vehicle to build trust between patient and care provider and for the patient to understand their fundamental role in the care team.

Multidisciplinary team: A multidisciplinary team is often involved to appropriately manage this complex condition. The infrastructure of such collaborative practice model should be built in an AF-clinic and requires collaboration and communication between multiple specialists that can be involved in the management of AF. Moreover, integration of specialized hospital care and primary health care is crucial to warrant continuous delivery of care and structured follow-up in the appropriate setting, with important roles for nurses and allied health professionals in terms of patient education and coordination of care.[9]

Use of technology: The use of smart technology is helpful for health care professionals (e.g. decision support technology, telemonitoring or mHealth) as well as for patients (e.g. disease specific educational applications, monitoring technology).[10,11] These applications aim to encourage integrated AF management whether it is by supporting decision making in the treatment team or empowering patients to monitor their vital parameters and self-manage their condition.

Comprehensive treatment and access to all treatment options: The management of AF should cover all domains of AF treatment as described before, however the composition and content of these domains will differ per individual patient and the availability of resources.

These fundamental aspects of integrated care are the basic infrastructure of integrated, specialized AF-clinics. In our institution the AF-clinic was developed a decade ago and has demonstrated clinical value,[12-14] and international guidelines have adopted this approach which is recommended as the Gold Standard management approach for AF.[2] The TeleCheck-AF approach underlines the multifaceted character of AF management. The mHealth intervention puts the patient 'in charge of their own care', by asking them to prove vital data in order to determine the best possible treatment. Engagement with the patient and providing clear instructions is key,

which commences before the teleconference. Within the teleconsultation, dedicated AF treatment - based on the data provided by the patient - will be provided as part of a comprehensive AF management approach provided by a multidisciplinary team.

IMPLEMENTATION OF TELECHECK-AF IN AN INTEGRATED AF CARE APPROACH

Who is eligible?

Heart rate and rhythm assessment in the TeleCheck-AF approach is based on PPG measures by an app. As diagnosis of AF still requires a documentation of an AF episode by electrocardiogram,[2] TeleCheck-AF is mainly appealing for the remote management of patients with previously documented AF. We identified several clinical scenarios in which TeleCheck-AF could support AF management through teleconsultations during the COVID-19 pandemic. First, for the assessment of heart rate and rhythm in patients scheduled for an outpatient clinic visit. Second, to guide rate control in patients who report with symptomatic (hemodynamically stable) recurrent AF episodes to the general practitioner, outpatient clinic or emergency department. Third, since no holter recordings are available during COVID-19, the approach can be used to assess rate and rhythm after ablation for AF and fourth, to up-titrate beta-blockers in patients with heart failure. In addition to assessment of heart rate and rhythm, the app also provides information on symptom-rhythm correlation by simultaneously assessing symptoms.

TeleCheck-AF patient instruction

Instruction and education of patients are key factors for successful implementation of the remote on-demand heart rate and rhythm monitoring for the management of AF patients. A case coordinator (e.g. a secretary or nurse) has an important role in clearly instructing the patient about why, how and when to use the app.

Why: The case coordinator explains that due to COVID-19 pandemic all face-to-face consultations are transferred to teleconsultations and that an ECG cannot be performed to assess heart rate and rhythm. Therefore, an mHealth-prescription to use the FibriCheck® app is provided.

How: The case coordinator provides instruction which includes an installation manual together with the activation QR-code which is sent to the patient by e-mail **(Figure 1)**. The case coordinator evaluates after 24 hours in the cloud if patients were able to activate the app and to perform measurements **(Figure 2)**. In case patients need further support, the case coordinator or the helpdesk of FibriCheck® can be contacted.

When: The provided patient manual instructs the patient to perform three measurements a day and in case of symptoms for a period of 7 days before the teleconsultation. In addition, patients are asked to assess their body weight and blood pressure, if possible, on a daily basis and provide the measurements during the teleconsultation.

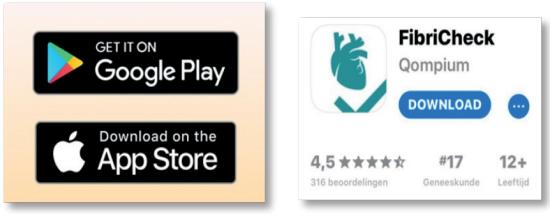
The on-demand mHealth approach is critically dependent on the willingness and adherence of the AF patients to perform the measurements. Besides education and engaging patients in their own AF management several features implemented in the app improve the adherence in TeleCheck-AF. On a daily basis, an automatic pop-up message is sent to the patients as reminder to perform heart rate and rhythm measurements. Additionally, the time-period of 'only' 7 days and the straightforward, simple and short measurement procedure (maximum two minutes) makes this approach very acceptable for patients.

Implementation of heart rate and rhythm information into teleconsultation

After 7 days the QR-code expires, and the data collection stops. In the cloud an automatic report is generated containing a summary of all measurements including heart rate, rhythm and symptoms.

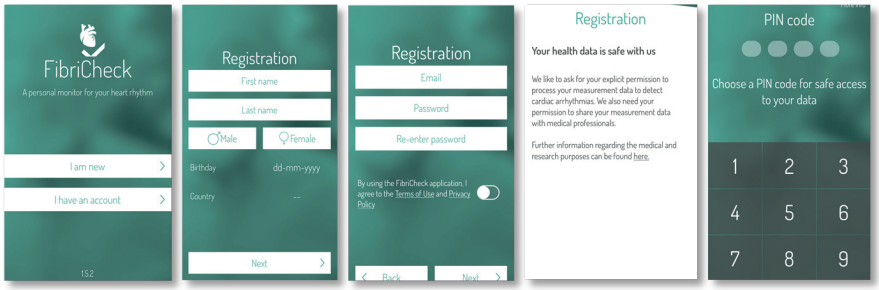
Step 1.

- Go to the "play store" or the "Apple App Store" on your smartphone.
- Search the app **'FibriCheck'** and download the application.



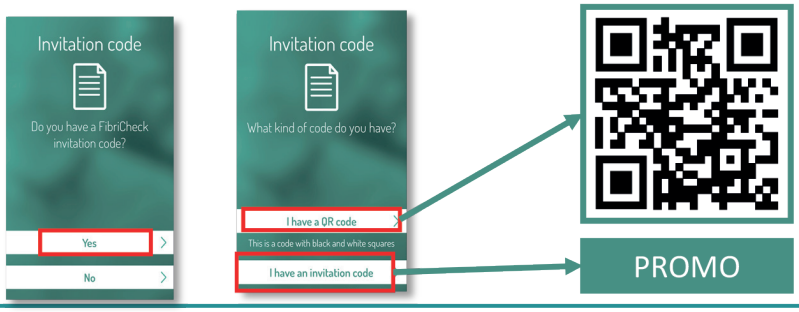
Step 2.

After the first-login you'll need to create an account, fill in your own personal data and the email address you provided to us.



Step 3.

- Do you have a FibriCheck invitation code?" -> Answer this question with **"YES"**
- Click on "I have a QR code", point the camera towards the QR code shown here.



Step 4.

- To perform a registration of the heart rhythm, click "start"
- Place your index finger "gently" on the camera of your smartphone (you do not need to cover the flashlight, this can become hot!). The registrations will start automatically and will take 60 seconds. Afterwards the data is automatically sent to your caregiver.

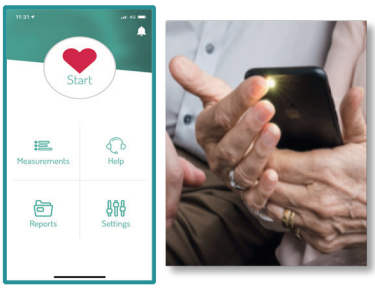


Figure 1. Installation manual including the QR-code for activation. *This manual provides a step by step approach to download the app and how to perform a measurement.*

Additionally, all healthcare professionals have access to the raw PPG traces of their patients via the cloud. Before the planned teleconsultation the physician logs into the cloud and can easily assess heart rate, rhythm and symptoms recorded by the patients during the week before which can be used to guide AF-management during the teleconsultation **(Figure 3)**. If needed, patients are asked to repeat the measurements for one more week to check if medication changes for rate and rhythm control were effective or not. For this they receive a new QR-code which then can be activated and a follow-up teleconsultation will be planned. Structured and comprehensive risk assessment and management is an important part of TeleCheck-AF during the teleconsultation. Based on self-reported body weight and blood pressure, obesity and hypertension can be managed, and general lifestyle changes recommended (**Table 1**).

Table 1. **Structured teleconsultation.**

Structured teleconsultation
Remote assessment of heart rate and rhythm
Detailed history taking
Stroke risk assessment (CHA_2DS_2-VASC score)
Self-reported risk factor assessment
Hypertension
Obesity
Additional risk factor assessment
Glucose, kidney function, hypercholesterolemia and thyroid function if needed in collaboration with general practitioner
Education and lifestyle advise
AF management: Adaptation of rate control, anticoagulation treatment

In addition to healthcare professionals, also the app facilitates education by providing information on AF, risk factors, lifestyle, heart failure and stroke risk (**Figure 4**). Further, education about the importance of lifestyle and risk factor management as well as treatment adherence is provided by online information material (e.g. www.getsmartaboutafib.net).

DISCUSSION

In recent online statements on the European Society of Cardiology website as well as in consensus papers on the guidance for the management of AF patients during the COVID-19 pandemic from the Heart Rhythm Society, American College of Cardiology and American Heart Association,[16] the use of telemedicine and mHealth solutions for remote patient care are recommended. However, a universal solution to allow wide and fast implementation of mHealth infrastructures is not provided. Herein, we describe our TeleCheck-AF approach incorporating a remote on-demand app-based heart rate and rhythm monitoring infrastructure and a comprehensive AF management approach through teleconsultation.

TeleCheck-AF includes fundamental components of a comprehensive integrated care approach (**Central Figure**). The patient is actively involved in the treatment trajectory by monitoring heart rate and rhythm information, as well as blood pressure and weight measures. Education about AF management and the importance of lifestyle and risk factor management is provided by a multidisciplinary team during teleconsultations. Also, there is a focus on empowering patients to self-manage these conditions which includes treatment adherence. Moreover, the app provides push notifications with information about their condition and the importance of adhering to the

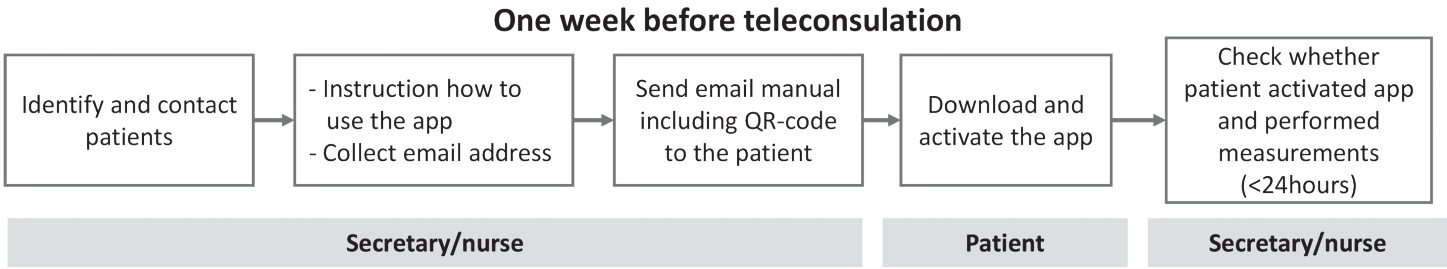


Figure 2. Organisation of the care pathway, preparation phase. *One week before the teleconsultation the physician identifies eligible patients. Subsequent, the secretary or nurse contacts the patient and explains that the face-to-face consultations is transferred to teleconsultation due to the COVID-19 pandemic. An e-mail including the manual and QR-code is sent to the patient; after 24 hours the secretary/nurse check whether the patient activated the app.*
Adherence

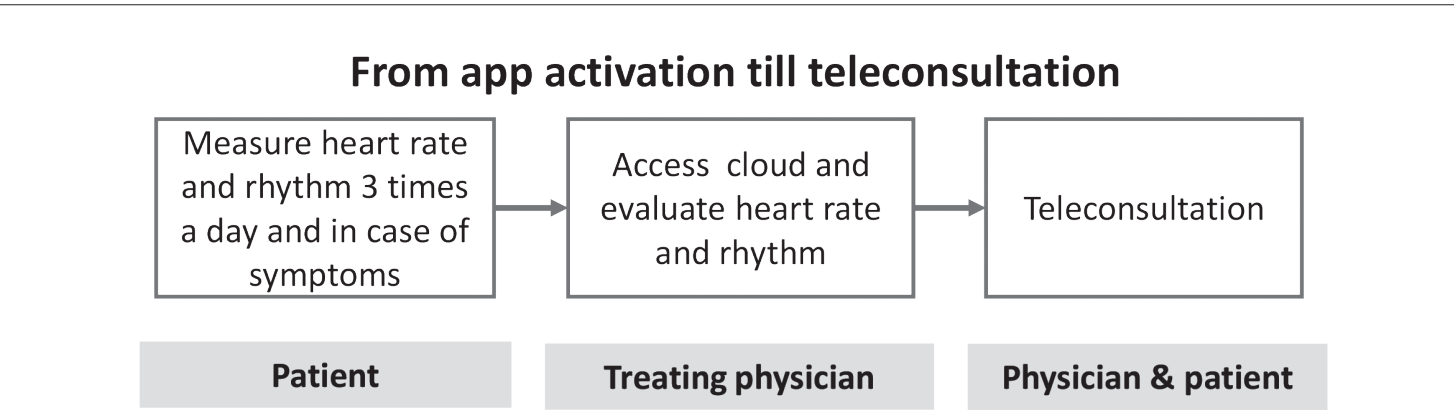
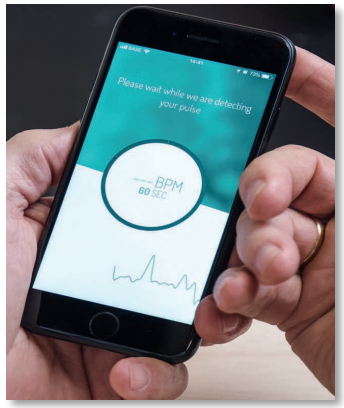
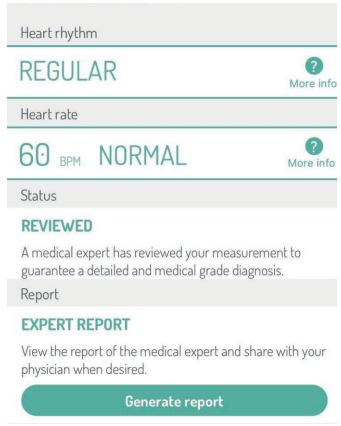


Figure 3. Organisation of the care pathway. *During one week before the teleconsultations patients are asked to measure three times a day and in case of symptoms. Before the teleconsultation the treating physician logs into the cloud to evaluate the measurement.*

A



B



C

How do I perform a good measurement?

We list some tips for you to help you to perform a good measurement:

Tip 1: Sit down quietly

Sit quietly, let your arms rest on a flat surface (e.g. a table) during the measurement, stay still and try not to talk.

Tip 2: Don't apply too much pressure on the camera

Do not apply too much pressure when placing your finger on the camera. Just a gentle touch is fine! If you press too hard, FibriCheck will not be able to analyse your measurement.

Tip 3: Remove the case of your smartphone

If you have a protective case around your smartphone please remove it. This improve the contact between your finger and the lens of the camera.

Tip 4: Cover the lens of the camera, not the flash

There is no need to place your finger on the flash. The light can get hot in certain cases.

Tip 5: If there are multiple cameras

The camera closest to the flash is most of the time the correct camera.

Help

D

Education

- Prevention
- Lifestyle
- Complications
- Risks
- Causes
- Different types of atrial fibrillation
- Symptoms
- Atrial fibrillation
- The heart

Legend of Figure 4. Usage of the FibriCheck. ***Panel A*** *shows an example of performing a measurement.* ***Panel B*** *shows a report after a measurement.* ***Panel C*** *demonstrates instructions to improve the quality of a measurement.* ***Panel D*** *summarizes the topics of the education provided by the FibriCheck app.*

treatment regimen. This supports self-management and ensures a regular data collection. The app is a true example of mHealth impacting both the patient (i.e. patient involvement by active role to provide data on rate and rhythm and reminding to adhere to the treatment regimen), as well as the health care professional (i.e. validated insights in rate and rhythm). During COVID-19, the accessibility to elective interventions and procedures such as electrical cardioversion as well as elective invasive interventions such as AF ablation is limited.[15] Nevertheless, remote adaptation of rate and rhythm medication guided by the on-demand monitoring infrastructure together with a comprehensive risk factor management, which has been shown to maintain sinus rhythm and reduce the need of AF ablation,[16] are elemental parts of TeleCheck-AF and helps managing AF patients during the COVID-19 pandemic.

The on-demand mHealth application for a limited predefined time period of 7 days prior the scheduled teleconsultation within the TeleCheck-AF approach is novel and differs from previous settings where mHealth is typically used for a longer rhythm monitoring period or provide decision support, risk assessment and patient education according to existing guidelines.[7,17,18] The goal in TeleCheck-AF is to make heart rate and rhythm information available, to allow a better assessment of the disease state of the patient and to support in treatment decisions through teleconsultation. The limited validity, regulated by a QR code, avoids unnecessary data-load. Additionally, maintenance costs associated with long term use of apps do not occur with an on-demand approach, which makes this TeleCheck-AF approach available for low costs.

An app-based approach has several advantages over device-based or wearable-based approaches during the COVID-19 pandemic. No hardware is required which has several hygienic and logistical advantages. The heart rate and rhythm monitoring infrastructure in TeleCheck-AF is a complete stand-alone unit, does not require any installation of software on a computer and can be combined in a flexible way with teleconsultation via telephone conversation, videoconferencing or videotelephony. A potential disadvantage is, that an electrocardiogram (ECG) cannot be provided; however the FibriCheck app algorithm is able to validly inform about the presence of AF and current heart rate.[6]

The broad accessibility of the mobile phone app used in TeleCheck-AF allows a fast implementation of the herein described mHealth infrastructure during the COVID-19 pandemic. Currently, MUMC+ makes the TeleCheck-AF infrastructure available in numerous large European centers focused on AF management within the TeleCheck-AF project. The TeleCheck-AF project was initiated on the 04 April 2020. The motto is: "Let´s keep our AF patients out of the hospital during COVID-19!". The goal is to maintain and secure AF care during COVID-19 and we are currently inviting other European centers to participate in this project.[19] For more information visit our website: www.telecheck-af.com and follow #TeleCheckAF on Twitter.

PERSPECTIVES AND CHALLENGES

In the TeleCheck-AF project, we aim to show that the TeleCheck-AF approach can be easily implemented and used in different European centers during the COVID-19 pandemic. Besides other factors, the lack of uniform European-wide legislations for telepresciption of drugs, digital health and reimbursement models have largely prevented the widespread use and broad clinical implementation of digital health services.[20] Hopefully the challenges of COVID-19 may help speed up the discussions with health insurances, hospitals and industry partners are required to allow

broader clinical implementation of this infrastructure in the future.[20] Whether TeleCheck-AF represents a streamlined and cost-effective monitoring system after the COVID-19 pandemic should be evaluated. For this, further study is warranted to test for efficacy, safety and durability of this approach.

CONCLUSION

Herein we describe a new mHealth approach facilitating AF management through teleconsultation. The TeleCheck-AF approach incorporates a structured teleconsultation, CE marked app-based on-demand heart rate and rhythm monitoring and integrated specialized AF management, and it can be easily implemented in European centers during COVID-19.

ACKNOWLEDGMENT

TeleCheck-AF was initiated by the Maastricht University Medical Center+ and is supported by FibriCheck and Biosense Webster.

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N.A.H.A. Pluymaekers,[+] R.M.J. van der Velden,[+] A.N.L. Hermans,[+] M. Gawałko, S. Buskes, J.J.H.M.W. Keijenberg, B. Vorstermans, H.J.G.M. Crijns, J.M. Hendriks,[*] D. Linz.[*]

[+]Shared first authorship *Shared last authorship

Cardiology 2021;146:392-6.

On-demand mHealth infrastructure for remote rhythm monitoring within a wait-and-see strategy for recent-onset atrial fibrillation: TeleWAS-AF.

ABSTRACT

Recently, we introduced the TeleCheck-AF approach, an on-demand mHealth infrastructure using app-based heart rate and rhythm monitoring for 7 days, to support long-term atrial fibrillation (AF) management through teleconsultation. Herein, we extend the mHealth approach to patients with recent-onset AF at the emergency department (ED). In the proposed TeleWAS-AF approach, on-demand heart rate and rhythm monitoring is used to support a wait-and-see (WAS) strategy at the ED. All stable patients who present to the ED with recent-onset symptomatic AF and who are able to use mHealth solutions for heart rate and rhythm monitoring are eligible for this approach. Patients will receive both, education on AF and instructions on the use of the mHealth technology before discharge from the ED. A case coordinator will subsequently check whether patients are able to activate the mHealth solution and to perform heart rate and rhythm measurements. At 40 hours after AF onset, the first assessment teleconsultation with the physician will take place, determining the need for delayed cardioversion. After maximal 7 days of remote monitoring, a second assessment teleconsultation may occur, in which the rhythm can be reassessed and further treatment strategy can be discussed with the patient. This on-demand mHealth prescription increases patient involvement in the care process and treatment decision making by encouraging self-management, while avoiding excess data-load requiring work-intensive and expensive data management. Implementation of the TeleWAS-AF approach may facilitate the management of AF in the ED and reduce the burden on the ED system which enhance the capacity for health care utilization.

INTRODUCTION

Several mobile health (mHealth) solutions have been recently introduced to screen for and to support management of atrial fibrillation (AF).[1] In response to cancellations of outpatient services and conversion into teleconsultations as part of the COVID-19 restrictions, we developed the TeleCheck-AF approach, which is an on-demand mHealth infrastructure incorporating an app-based heart rate and rhythm monitoring to support remote AF management through teleconsultation. The approach has been described in detail elsewhere.[2,3]

Based on the feasibility of the TeleCheck-AF approach[2] we aim to extend the mHealth approach to the management of recent-onset AF in the emergency department (ED). Patients with recent-onset AF commonly undergo immediate restoration of sinus rhythm by pharmacologic or electrical cardioversion. However, the RACE 7 ACWAS (Rate Control versus Electrical Cardioversion Trial 7 – Acute Cardioversion versus Wait and See) study showed that a wait-and-see (WAS) strategy in patients with recent-onset AF (rate control for symptom relief followed by delayed cardioversion if needed <48h) allows spontaneous conversion to sinus rhythm in 69% of patients, obviating active cardioversion.[4] Recurrences within one month were seen in 30% of patients in both groups, i.e. the initially chosen strategy did not affect the recurrence pattern.[4] The WAS approach is now also mentioned as an option to manage patients with recent-onset AF in the current ESC Guidelines for the diagnosis and management of AF.[5] However, a clear practical guidance for this WAS approach and advice how to perform rhythm monitoring is not provided.

In this manuscript we describe the implementation of the TeleWAS-AF approach, an on-demand mHealth-based heart rate and rhythm monitoring infrastructure to support a WAS strategy for patients presenting with recent-onset AF at the ED.

METHODS

Implementation of TeleWAS-AF in an emergency department

An overview about the TeleWAS-AF approach, the different steps during the decision-making process and the subsequent assessment teleconsultations are summarized in **Figure 1**.

Who is eligible for a WAS strategy supported by TeleWAS-AF?

All patients who present to the ED with an episode of recent-onset (<36 hours) symptomatic AF (or atrial flutter or atrial tachycardia), documented on an electrocardiogram (ECG) without signs of acute heart failure, acute myocardial infarction or haemodynamic instability, and who are able to operate mHealth solutions for heart rate and rhythm monitoring and own a smartphone are eligible to the TeleWAS-AF approach.

There are two scenarios how an eligible patient may present to the ED: (1) Patients with recent-onset AF who directly present to the ED with symptomatic AF. (2) The general practitioner or a medical specialist refers a patient with a recent-onset AF episode to the ED.

Patient education and instruction at the ED

Instruction and education of the remote on-demand heart rate and rhythm monitoring to patients is crucial for successful implementation of the mHealth approach. The multidisciplinary ED team, including nurses, a case coordinator and physicians have an important role in administering clear guidance to the patient about why, how and when to use the mHealth solution for heart rate and rhythm monitoring.

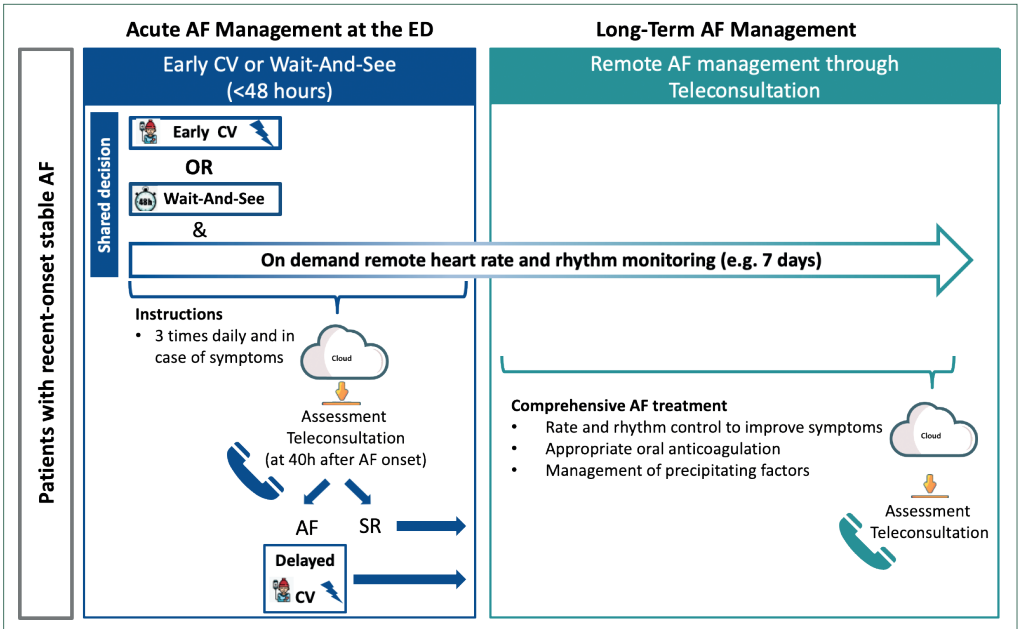

***Figure 1. Overview about the TeleWAS-AF approach, the different steps during the decision-making process and the subsequent assessment teleconsultations. ED** emergency department; **CV** cardioversion; **AF** atrial fibrillation; **SR** sinus rhythm.*

Patient education

The patient will be educated about AF, AF-related symptoms, possible complications and potential treatment options, specifically the acute treatment of AF, e.g. WAS strategy or early cardioversion. In almost 70% of the cases[3], the heart rhythm spontaneously recovers to sinus rhythm and immediate cardioversion is not needed (and therefore possibly resulting in the avoidance patients' overtreatment). In the case of the WAS strategy, heart rate lowering medication (such as beta blocker, verapamil, digoxin) can be prescribed to reduce complaints of AF, and afterwards the patient can await spontaneous conversion to sinus rhythm at home. To monitor the heart rate and rhythm during the WAS period, a mHealth solution, such as handheld devices (e.g. AliveCor, MyDiagnostick) or mobile apps (e.g. FibriCheck), connected to a cloud can be used for maximal 7 days after the ED visit (7-day mHealth-prescription).[1] In our initial pilot studies, we used the FibriCheck app using photoplethysmogram (PPG) technology through the smartphone's built-in camera, which can be downloaded on the patient's smartphone.[2,3]

Patient instruction

Why: The ED nurse explains that the mHealth solution is used for remote heart rate and rhythm assessment during the waiting period of the WAS strategy. Therefore, a 7-day mHealth-prescription to use a handheld device or an app is provided.

How: The ED nurse gives instructions to the patient on how to use the handheld device or install the app on the smartphone and a patient manual is provided.

When: The provided patient manual instructs the patient to perform three measurements of heart rate and rhythm a day (morning, afternoon, evening) and additional measurements in case of symptoms during days until the teleconsultation with the treating physician.

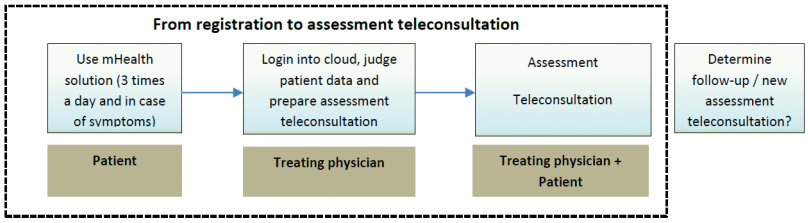

Figure 2. Organisation of the care pathway. *Patients are asked to measure heart rate and symptoms by the mHealth solution three times a day and in case of symptoms. Before the assessment teleconsultation the treating physician logs into the cloud to evaluate the measurement.*

Implementation of heart rate and rhythm information into the assessment teleconsultations

The case coordinator checks the cloud if patients are able to activate the handheld device or the app and to perform heart rate and rhythm measurements. In case patients need further support, the case coordinator can be contacted. The telephone number of the ED for urgent matters is provided in the patient manual. All healthcare professionals have access to the raw rhythm traces of their patients via the cloud. Prior to teleconsultation the physician logs into the cloud and can assess heart rate, rhythm and symptoms recorded by the patients. The flowchart of the assessment teleconsultations is provided in **Figure 2.**

First assessment teleconsultation at 40h after AF onset: If the telemonitoring recordings suggest sinus rhythm, no further action is required, patients will continue their heart rhythm and rate recordings. If AF remains to be present, a cardioversion may be performed within 48 hours after AF onset.

Second assessment teleconsultation at 7 days: After maximal 7 days of the mHealth-prescription the handheld device or the app expires, and the data collection stops. If the recordings suggest sinus rhythm, no further action is required. If AF remains to be present or AF recurrence occurs, the subsequent strategy can be further discussed together with the patient. A cardioversion can be performed. Alternatively, pharmacological rate and/or rhythm control can be optimized including AF catheter ablation. In this case, patients are asked to repeat the measurements for one more week to check if medication changes for rate and rhythm control were effective or not. For this they receive a new mHealth-prescription which then can be activated, and a follow-up assessment teleconsultation will be planned.

According to the current ESC AF guidelines, the following points need to be considered in regard to a WAS strategy.[5] (1) In anticoagulated AF patients, a WAS strategy can be applied irrespective of duration of the current AF-episode. (2) In patients with recent-onset AF with a definite duration of AF <48 hours, an early cardioversion can be performed irrespective of anticoagulation. (3) If a cardioversion is performed: In hemodynamically stable patients with symptomatic AF, the choice between electrical and pharmacological cardioversion should be guided by patient and physician preferences aligned with guideline recommendations. (4) In patients at risk for stroke, anticoagulant therapy should be continued long-term after cardioversion according to the long-term anticoagulation recommendations, irrespective of the method of cardioversion or the apparent maintenance of sinus rhythm. In patients without stroke risk factors, anticoagulation is still under debate and is recommended for 4 weeks after cardioversion by some societies (e.g. the Canadian Cardiovascular Society[6]). (5) If a cardioversion is intended in patients with >48h recent-onset AF without anticoagulation, a transesophageal echocardiography to exclude an atrial thrombus or effective anticoagulation for a minimum of 3 weeks is recommended.

DISCUSSION

There are several points which make the TeleWAS-AF approach unique. Experiences within integrated AF-care, active patient involvement in the care process as well as in the treatment decision is crucial. In fact, patients take responsibility of their care and health care professionals rely on the self-care of patients (i.e. measuring heart rate and rhythm and reporting on experienced symptoms). Therefore it is of significant importance to prepare patients for such role, by means of three E's: *Engagement*: identify the patient's needs, values and preferences; provide clear *Education* and instruction in a way that patients understand what is expected from them; *Encourage* them to undertake self-management (i.e. measuring vital parameters) and involve them in informed or shared decision-making regarding their AF treatment. This novel approach may require significant changes and redesign in the delivery of care.[7]

Heart rate and rhythm monitoring in the TeleWAS-AF approach can be performed by handheld devices or app-based mHealth solutions using ECG or PPG technology. In general, the PPG technology has limitations in diagnosing AF, as current AF guidelines require an ECG documentation of an AF episode.[5,6] TeleWAS-AF is exclusively used in patients who present with recent-onset AF and get a documentation of the AF episode at the ED. Therefore, the PPG-based app is not used for the diagnosis of AF, but for the heart rate and rhythm assessment within the WAS strategy.

The limited validity for maximal 7 days, regulated by a 7-day mHealth prescription, avoids unnecessary data-load requiring work-intensive and expensive data management. If an app-based mHealth solution is used, no hardware is required which has several hygienic and logistical advantages and makes this TeleWAS-AF approach available at low costs.

CONCLUSIONS AND FUTURE IMPLICATIONS

Herein we describe a new mHealth approach facilitating acute management of recent-onset AF by a WAS strategy, which will impact the management of AF in the ED system. Whilst maintaining the delivery of comprehensive treatment, the approach has potential to reduce the burden on EDs and enhance the capacity for health care utilization. However, given the change in treatment approach, redesign of care delivery and reimbursement models may be warranted. Obviously, the patient's role in the decision-making process and the communication between patient and treatment team is crucial. Short term, we will communicate this approach to all participating centers of the TeleCheck-AF project within the following weeks.[3] Long-term, we are currently conducting a multicentre randomised clinical trial RACE 9 OBSERVE AF (Reg number NL73104.068.20) in which a device-based watchful-waiting strategy, i.e. symptom reduction through rate-control medication and monitoring for four weeks until spontaneous conversion is achieved compared to standard care, consisting of either early or delayed cardioversion according to the TeleWAS-AF approach.

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General discussion

CARDIOVERSION FOR ATRIAL FIBRILLATION

In this thesis the central question is whether we should revisit current cardioversion practices for atrial fibrillation (AF). Although cardioversion does not seem to impact the long term outcome of patients with AF[1,2], it has a pivotal role in the management of AF and is an often performed procedure to alleviate symptoms. Cardioversion can be accomplished either by pharmacological cardioversion (PCV) or electrical cardioversion (ECV), or a combination of both. Pharmacological cardioversion consists of the administration of anti-arrhythmic drugs (AADs) orally or intravenously. Based on their mechanism AADs are classified according the Vaughan Williams classification in five classes[3]. For rhythm control mainly class I (sodium channel blockers) and class III (potassium channel blockers) are recommended, the specific choice of drug depends on the severity of concomitant cardiac diseases[4]. PCV is more effective in patients with paroxysmal AF (success range around 59-89%) but can also be used to enhance success rate of ECV in persistent AF[5-8]. Adverse effects of AADs are hypotension, QT prolongation, QRS widening, (non-sustained) ventricular tachycardia, phlebitis, and bradycardia or atrioventricular block[4].

Electrical cardioversion is more effective than PCV (success range around 78-96%) and consists of an external or internal delivered direct current. For external ECV adhesive electrode patches are placed in anterior-lateral or anterior-posterior position on the thorax. Internal ECV can be performed in patients with implantable cardioverter-defibrillators (ICDs). However, the success rate is low compared to external ECV and therefore external ECV is preferred[9,10]. Although, one of the concerns was that external ECV may have adverse effects on leads and devices in patients with pacemakers or ICDs. In a retrospective analysis we evaluated the safety of external ECV in patients with cardiac implantable electronic devices (CIEDs). Our results suggest that external ECV can be performed safely in patients with contemporary CIEDs respecting the recommendations of the ESC guidelines to use biphasic shock waveforms and an anterior-posterior paddle position (**Chapter 8**). This is also confirmed in a randomized trial of Lüker et al. in which internal ECV was compared to external ECV. Besides that external ECV seems more effective they found no clinically meaningful adverse events as a result of external ECV[9]. Also in patients without CIEDs, ECV can be related to adverse effects. For instance, patients need to be sedated before the procedure, this could lead to sedation related complications. Further, hypotension, ventricular fibrillation due to shock administration during ventricular repolarization, bradycardia (i.e. underlying sick sinus syndrome), and thermal skin injury can occur[11,12]. Although some of those complications can be life threatening, in general the above mentioned complications for both PCV and ECV are rare[12].

In clinical practice, the approaches for cardioversion vary greatly[13]. For recent-onset AF immediate PCV or ECV has been the default strategy at the emergency department[13-15]. Considering the possible complications of cardioversion and the fact that recent-onset AF often terminates spontaneously[16-21] the question is whether this aggressive rhythm control approach is necessary at all for those patients.

In part I of this thesis, the results of a systematic review on the frequency and determinants of spontaneous conversion (SCV) is discussed and reflects a wide range of SCV from 9 up to 83%. One of the observations was that a higher SCV rate was seen if a sufficiently long observation period was used, since most patients convert spontaneously within the first 24-48 hours (**Chapter 3**). We tried to identify patients with a high likelihood of SCV, since this could improve a personalized AF management and prevent overtreatment with cardioversion. Possible clinical determinants of early SCV at the ED were evaluated in **Chapter 2**. In this cohort of 943 patients who presented with AF at the ED we found a duration of AF <24 hours, a first episode of AF, a lower left-atrial volume index (LAVI), a lower body-mass index (BMI), a longer QTc time during AF and symptoms of near-collapse at presentation as determinants of early SCV. These parameters are most likely indicative of early phases of AF evolution. A lower LAVI suggests that macroscopic electrical and structural remodelling

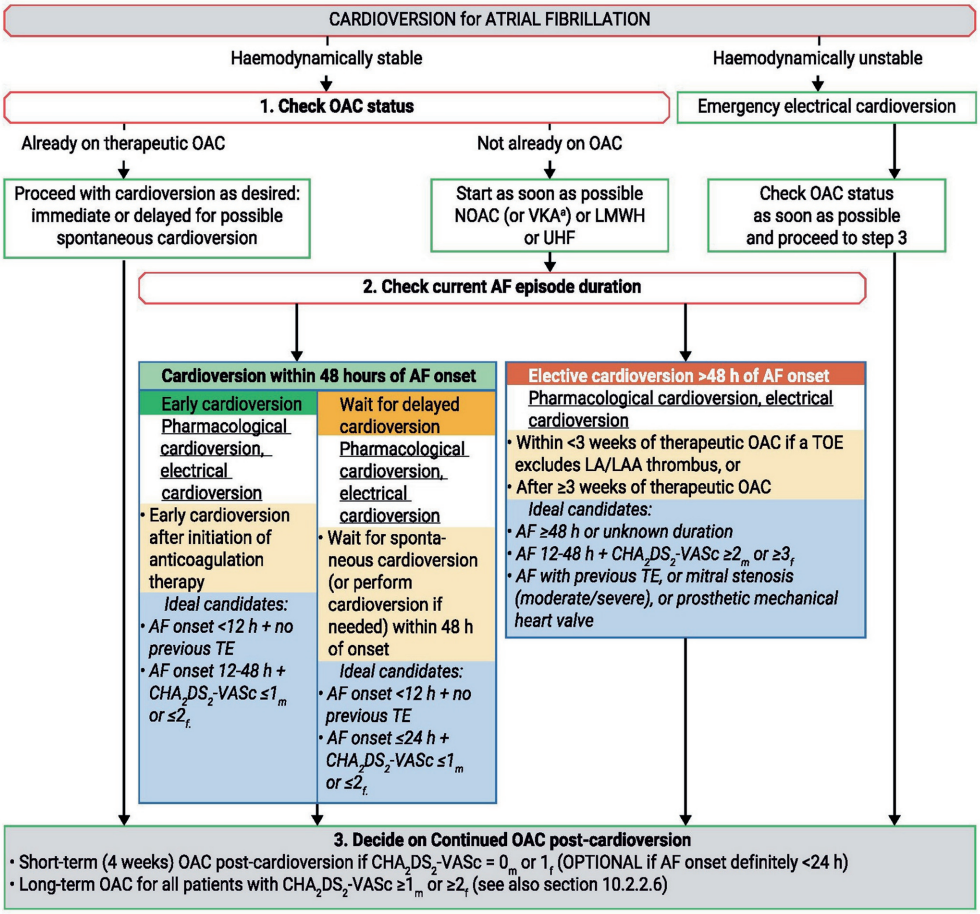

Figure 1. Flowchart for decision making on cardioversion of AF depending on clinical presentation, AF onset, oral anticoagulation intake, and risk factors for stroke. *Hindricks, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2021;42:373-498, reprinted with permission of Oxford University Press.*

of the atria is evident yet or is at an early stage. Obesity is a well-known risk factor for developing AF[22] and a higher BMI is independently associated with progression from paroxysmal to permanent AF[23]; this could explain the higher SCV rate in patients with a lower BMI. Patients presenting with near-collapse during AF more often had first-detected AF, which may be related to the higher SCV rates seen in those patients. In this manuscript we identify determinants of 'early' SCV (<3hours after presentation to the ED), but those may differ from determinants of SCV if a longer observation period is allowed. Therefore, we evaluated all determinants of SCV in our systematic review **(Chapter 3)**. We observed a high variation of determinants of SCV between studies, which probably related to relatively small patient numbers per study and different strategies when including specific variables in the prediction models. Nevertheless, the most important determinants of SCV include short duration of AF (<24 or <48 hours versus longer duration at ED presentation, although that was not supported by all studies)[16,18,24], low episode number (first-detected AF versus recurrent

AF or previous supraventricular arrhythmias), normal atrial dimensions, and absence of previous heart failure or other underlying heart diseases. So one can conclude that spontaneous conversion occurs frequently in patients with recent-onset AF and more often in patients with first-onset, short-duration AF episodes, lower BMI, absence of underlying heart disease and normal left atrial size, which all may reflect to an early phase of AF evolution.

The majority of the included studies in our review evaluated SCV during a hospitalized observation period and did not report safety aspects. In the second part of this thesis the result of a multicenter randomized controlled trial on a novel wait and see approach, which allows SCV for recent-onset AF, is described.

The wait-and-see approach for atrial fibrillation

Considering the high spontaneous conversion rate in patients with recent-onset AF, an initial approach with rate control to alleviate symptoms and await spontaneous conversion at home might be a good alternative to early cardioversion[25]. In the multicenter, randomized trial, RACE 7 ACWAS (Rate Control versus Electrical Cardioversion Trial 7–Acute Cardioversion versus Wait and See) we showed that a wait-and-see approach (with initial rate control to alleviate symptoms and delayed cardioversion only if needed at 48 hours) is non-inferior to early cardioversion (PCV or ECV) in terms of achieving sinus rhythm at four weeks (**Chapter 4**). Notably, in the wait-and-see approach (also referred to as delayed cardioversion approach) almost 70% of the patients converted spontaneously to sinus rhythm within 48 hours after onset of symptoms obviating the need for cardioversion. This trial has led to a change in the cardioversion guidelines for recent-onset AF, which now includes a wait-and-see approach as alternative option for patients with stable recent-onset AF[4]. **(Figure 1).**

The wait-and-see approach does not replace early ECV but provides a good and safe alternative. Physicians and patients should choose between the two approaches in a shared decision making process since both approaches have several advantages. Pharmacological cardioversion allows to observe the 'diagnostic' AAD responses like drug-induced conduction abnormalities, ventricular arrhythmias or Brugada ECG[26]. This enhances clinical management in general as well as safety and applicability of pill-in-the-pocket home-cardioversion of recurrent AF[27] (**Chapter 6.1**). Similarly, ECV can unmask sick sinus syndrome[11] and like PCV shortens time till conversion compared to wait-and-see. On the other hand, allowing AF to convert spontaneously contributes to a better classification of AF, which may benefit long-term management. Another important advantage of the wait-and-see approach is that patients can experience that the arrhythmia terminates spontaneously, and considering AF is often a recurrent phenomenon this may improve self-management and may reduce future ED visits for AF and thereby costs. In the one year outcome results of the RACE 7 ACWAS trial (**Chapter 7**) we observed a trend in less ED visits for recurrent AF in the wait-and-see group although this was not statistically significant. Possible explanation for this could be that both groups (wait-and-see and early cardioversion) received the same education and information on self-terminating AF and how to deal with it.

One could hypothesize that a wait-and-see approach with delayed cardioversion reduces costs since it reduces the number of cardioversion procedures and if elective cardioversion is still required, these procedures can be scheduled during dedicated timeslots outside the overcrowded ED. Our study showed a trend towards lower costs in the wait-and-see group but this was not statistically significant (**Chapter 7**). This may be due the fact that we could not account for duration of ED visits which would favour a delayed cardioversion approach. Another reason could be due to more PCVs in the early cardioversion group which is relatively cheap compared to ECV which requires the involvement of nurses, an anaesthesiologist and a cardiologist or emergency physician. Further refinement of the wait-and-see approach should focus on optimizing the logistic pathway with introduction of remote heart rhythm assessment which can prevent recurrent visits to the ED and thereby reduces costs (Part 4 of this thesis).

Another important observation was that a wait-and-see approach did not negatively affect the quality of life of patients compared to the early cardioversion group. Also we did not observe an excess of major adverse events (**Chapter 7**). This is in line with previous trials comparing rate and rhythm control for AF[1,2,28,29]. Notably, recent studies showed that early rhythm control may be beneficial but those studies dealt with early initiated chronic rhythm control in ambulatory AF patients rather than early rhythm control in acute AF[30,31]. Therefore, we believe studies are not at odds and strategies may complement each other. E.g., adopting wait-and-see for a recurrent episode of AF provides information on spontaneous conversion which may inform the decision making process concerning chronic rhythm control treatment.

Wait-and-see approach and progression of atrial fibrillation

Several studies showed that progression of AF is associated with worse outcome[32-36]. Therefore, an early rhythm control approach might be applied to prevent progression from paroxysmal to persistent AF. While focal activity from the pulmonary veins frequently underlies the initiation of paroxysmal AF[37], the maintenance of the arrhythmia and its progression to persistent AF is believed to relate to the degree of atrial substrate[38]. Atrial substrate as a result of electrical and structural remodeling can be caused by AF itself but may also relate to concomitant risk factors[33,35,38]. Also for recent-onset AF may hold that "AF begets AF"[39], and a potential advantage of shortening the time until conversion might be to prevent or attenuate the progression to persistent AF. Considering this, taking away the trigger and part of the substrate by catheter ablation may reduce AF progression[40,41], especially a rhythm control strategy early after diagnosis might be beneficial[42]. Importantly, we did not observe progression of AF in patients with longer times in AF in the wait-and-see arm compared to the control arm in the RACE 7 ACWAS trial (**Chapter 7**). The number of patients with MyDiagnostick-detected recurrent episodes within one month (**Figure 2**) and the number of patients in sinus rhythm after one year were similar in both groups. Further, the overall 1-year progression rate from paroxysmal to persistent or permanent AF in this study was moderate (8%) and in line with the natural time course of AF progression reported in previous studies[33-35,43]. This again underlines the importance of early risk factor assessment and management irrespective of rhythm control strategy[4,35,44-47]. Even though no difference in progression of AF in recent-onset AF is observed in our trial, future studies are needed to assess the long-term consequences of a wait-and-see approach on the progression of atrial remodeling. Whether a systematically maintained early cardioversion strategy will reduce AF progression remains to be seen but as reported was not apparent from our 1-year data. Currently, the RACE 5 (Reappraisal of Atrial Fibrillation: Interaction between hyperCoagulability, Electrical remodeling, and Vascular Destabilisation in the Progression of AF) registry is on-going which might provide insights on this question.

Need for reclassification of atrial fibrillation?

Despite the clear definition in the AF guidelines on the classification of paroxysmal AF (defined as self-terminating AF within 7 days) and persistent AF (defined as AF lasting longer than 7 days and requires cardioversion for termination)[4], clinically the differentiation between paroxysmal AF and persistent AF remains challenging. And even in patients with paroxysmal (self-terminating) AF the duration can vary over time within one patient. Therefore, the current classification seems not to reflect the heterogeneous and dynamic pattern of paroxysmal AF[48,49]. Wineinger and colleagues tried to improve this classification of self-terminating AF by analyzing 13.293 patients with paroxysmal AF with a single lead ECG patch for two weeks. They describe two different patterns of paroxysmal AF, the 'legato' and the 'staccato' type[48]. The staccato pattern reflects many and short AF episodes, while the legato pattern reflects a few and long episodes. The legato pattern was more common with increasing age[48]. More recently, an interim analysis of the RACE 5 registry was

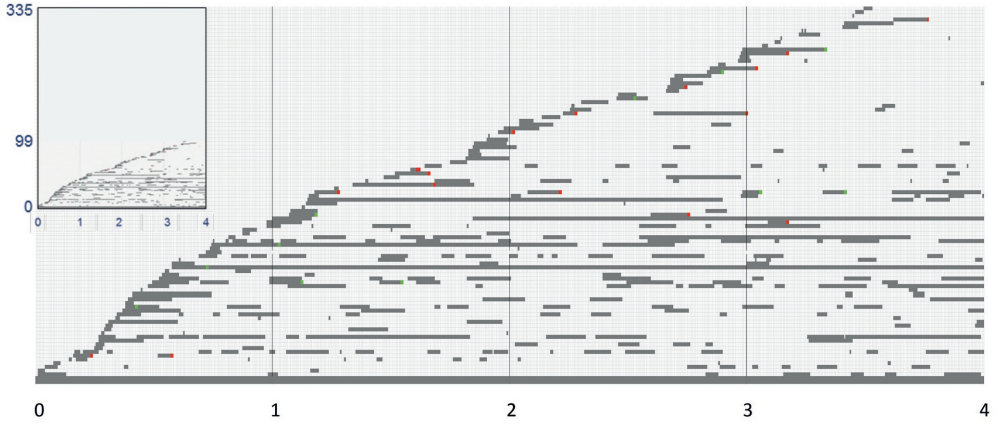

Figure 2. Overview of recurrent AF episodes documented with one lead ECG. *Telemetric ECG recordings were available for 335 patients (164 in the delayed-cardioversion group and 171 in the early-cardioversion group). Within 4 weeks after the index visit, a documented recurrence of atrial fibrillation occurred in 49 patients (30%) in the delayed-cardioversion group and in 50 patients (29%) in the early cardioversion group.*

performed in which 202 patients with paroxysmal AF were followed with continuous rhythm monitoring (implantable loop recorder or pacemaker) for 6 months. During follow-up 69% of patients experienced one or more recurrent episodes of AF, 99.9% of those episodes (11.456 of the 11.466 episodes) were self-terminating AF. The recurrent episodes were divided into short AF episodes (<6 hours), intermediate (6–12 hours), and long AF episodes (>12 hours). Patients with long AF episodes were more often men, had more underlying comorbidities, a larger waist circumference and higher left ventricular mass[49]. This is in line with the determinants of SCV, since those patients had often a relatively short duration of AF (but long enough to be recorded at a hospital's first aid), lower BMI, and less underlying comorbidities (**Chapter 2 & 3**).

Both studies tried to improve the classification of paroxysmal AF based on the duration of AF episodes. Since the duration of the episodes may reflect the progression of the disease this is a worthy alternative to consider. Unfortunately, both studies used different cut-off values which makes a comparison of the results difficult. Additionally, cut-off value which could be applied for the clinical classification of patients are not available. Interestingly, from the two studies it appears that paroxysmal self-terminating AF may last for several days. In the study of Wineinger et. al. the median AF duration per individual was 7.5 hours (IQR 2.4–18.6 hours) and some episodes may have lasted for weeks. Similarly, in the RACE 5 registry also self-terminating episodes of a few days were reported. Those long episodes of AF were more common in patients with more comorbidities which is a known contributor to the development of an AF substrate. Also in the RACE 7 ACWAS trial we observed different patterns of recurrent AF during one month follow-up with intermittent monitoring. Some patients had very frequent short episodes and some extended even over 7 days with spontaneous termination (**Figure 2**). In the LOOP trial, episodes longer than 24 hours were predicted by male sex, higher age, comorbidities, lower resting sinus rate and higher baseline body mass index, N-terminal prohormone of brain natriuretic peptide and troponin T[50].

Observing the natural course of AF may contribute to better characterize the phase of AF evolution and thereby improve a personalized AF management. In patients with short episodes (or staccato pattern), triggers may play a more important role compared to the atrial substrate. Targeting the trigger in an early phase (i.e. with ablation therapy) might be beneficial for patients

with recurrent episodes of the staccato type, and this may also explain the beneficial effect of rhythm control reported in the EAST-AFNET 4 trial[30]. The question remains however, what the exact cut-off should be in terms of duration of the episode and also in terms of beneficial effect from a rhythm control therapy. Clear is, that in all patients regardless the duration of the episode strict control and management of risk factors is crucial to prevent progression of AF. More studies with continuous or intense longitudinal rhythm monitoring are needed to investigate whether those subtypes of paroxysmal AF indeed exist and differ in pathophysiology, underlying risk factors, mechanism of termination or even prognosis.

Role of remote monitoring in cardioversion and future perspectives

As mentioned above, observing the natural course of AF could help identify the phase of AF evolution and thereby improve a personalized and tailored AF management. The wait-and-see approach allows this for patients who convert spontaneously within 48 hours of onset. The question remains however if we should perform a delayed cardioversion at 48 hours, since it is well known that paroxysmal AF can terminate spontaneous up till 7 days and even beyond[4,49,51]. Performing a delayed cardioversion withholds physicians and patients of observing the short-term natural course of the disease, limiting future personalized rate and rhythm control directions. Therefore, one could question whether we should apply a watchful-waiting approach instead of the current wait-and-see approach for patients with recent-onset AF. A watchful-waiting approach consists of administration of rate control medication to obtain symptom control during 4-week short-term follow-up. If AF is still present at four weeks, an elective cardioversion can be performed. We will investigate this in the currently on-going, randomized multi-center RACE 9 Observe AF trial (ClinicalTrials.gov NCT04612335). This watchful-waiting approach allows the observation of the natural course of AF but in order to implement this approach safely, an innovative remote rate and rhythm monitoring infrastructure must be installed which allows instantaneous treatment decisions on heart rate and rhythm.

In current practice, this remote heart rate and rhythm infrastructure to guide management in recent-onset AF patients is neither standard of care nor integrated in the current guidelines[14,15,52]. For the RACE 9 trial we developed a new device-based telemonitoring infrastructure enabling instantaneous monitoring and remote adjustment of rate and rhythm control therapies. This infrastructure contains an automatic red-amber-green alert system which also will contribute to earlier detection of brady- and tachyarrhythmias and early remote adjustment of rate and rhythm control. Our hypothesis is that the implementation of a watchful-waiting rate control strategy managed by remote rhythm monitoring for recent-onset AF will obviate the need for cardioversion, improve resource utilization in EDs, avoid overtreatment with cardioversion and reduce costs which will be elementary to sustain healthcare services in its current form.

During the implementation of this device-based infrastructure and the initiation of the RACE-9 trial, the COVID-19 pandemic resulted in an acceleration of mHealth use in Cardiology clinics[53]. Also in Maastricht, all face-to-face consultations in our AF clinic were changed to teleconsultations due to social distancing measures and government restrictions. Initially, we did not have any information on heart rate or rhythm of the patients available at the time of teleconsultation. We used a remote rate and rhythm monitoring in the TeleCheck-AF approach ("Tele": a structured teleconsultation "Check": an app-based on-demand heart rate and rhythm monitoring infrastructure, and "AF": comprehensive AF management), which is a remote on-demand monitoring infrastructure, which is based on a mobile phone app using photoplethysmography (PPG) technology allowing remote heart rate and rhythm monitoring and simultaneously symptom assessment **(Chapter 10-12)**. Beyond other clinical scenarios, we also used this approach to guide a wait-and-see approach, and thereby maintaining the delivery of a comprehensive treatment approach during the COVID-19 pandemic while potentially reducing the burden on EDs and with this enhance the capacity for health care utilization **(Chapter 12)**.

We reported our first results of thirty patients which confirmed that this infrastructure is feasible, convenient, broadly accessible and relatively low in costs **(Chapter 10 and 11)**. Within the TeleCheck-AF project, we implemented this TeleCheck-AF infrastructure in 40 centers throughout Europe[54] **(Chapter 11)**. An advantage of this PPG based infrastructure is that no hardware is required which has several hygienic and logistical advantages. A potential disadvantage is, that no electrocardiogram can be provided, but the algorithm used by the app can validly inform about the presence of AF and current heart rate.

This remote heart rate and rhythm infrastructure may also be beneficial to guide an elective ECV in patients with presumed persistent AF. In those patients an ECV can be used as a 'diagnostic' tool to identify a symptom-rhythm correlation[11]. Even though a large proportion of patients with AF reports symptoms, it often remains unclear whether all symptoms are related to AF or whether also other concomitant cardiovascular or non-cardiovascular conditions and risk factors contribute to overall symptom burden in an individual patient. We tried to observe this symptom-rhythm correlation in a prospective observational cohort of patients with persistent AF planned for elective ECV **(Chapter 9)**. The prevalence of a symptom-rhythm correlation around ECV was low and the symptom pattern often changed after ECV. One important limitation of this study was that the predominantly self-reported symptoms around ECV were obtained retrospectively from patient medical records and not simultaneously with rhythm information. Therefore, a remote heart rate and rhythm infrastructure could guide this 'diagnostic' ECV better by simultaneous recording of symptoms and rhythm before and after ECV. Besides this valuable information on symptom-rhythm correlation it also provides insights into the pattern of the arrhythmia since also patients with presumed persistent AF may have a self-terminating pattern (unpublished data). Further research is warranted to evaluate this strategy to assess symptom-rhythm correlation in patients with persistent AF and to establish the clinical implications of symptom-rhythm correlation assessment for AF management.

Both the RACE 9 Observe AF as well as the TeleCheck-AF approach will provide evidence that a remote heart rate and rhythm infrastructure based on 1-lead ECG or PPG signal enables the remote management of AF patients. This infrastructure should be flexible and easy adaptable to the emerging mHealth developments. In order to successfully implement such mHealth infrastructure also reimbursement solutions are required to allow long-term implementation of this infrastructure in the management of AF patients. The 'on prescription' use of mHealth as described in the TeleCheck-AF and RACE 9 approach is a new concept of mHealth use and differs from previous settings where mHealth is typically used for a longer rhythm monitoring period or provide decision support, risk assessment and patient education according to existing guidelines[55-57]. The 'on prescription' with limited period of use of the mHealth application, avoids unnecessary data-load which probably reduces costs and improves adherence.

Since AF is a chronic disease, the remote mHealth infrastructure as well as the watchful-waiting strategy will improve patient education about the recurrent and transient nature of AF and thereby improve acceptance of recurrent episodes of AF and self-management or their recurrent episodes and their AF management in general. Also, having the opportunity to communicate 'on-line' with their care team may reduce patients' anxiety and broaden their insight into treatment options. The latter may support future informed shared decision making and patient involvement. In turn, that may enhance cost-effectiveness of rate and rhythm control therapies for AF. The exact impact will be investigated in the RACE 9 Observe AF trial and the TeleCheck-AF project.

To conclude, the work presented in this thesis has contributed to the change of the guidelines on the management of recent-onset AF. Note that, cardioversion for AF could provide valuable information on symptom-rhythm correlation especially in patients with persistent AF. Although, for recent-onset AF the wait-and-see approach seems a reasonable alternative to early cardioversion and allows for spontaneous conversion and may lower health care costs. This observation of SCV

provides valuable information which can enhance the classification of AF and may thereby improve long-term rhythm interventions and outcome in those patients. Several determinants for SCV have been identified and could help identifying patients with a high likelihood of SCV, although in the RACE 7 ACWAS trial we observed that such algorithm lacks sensitivity and applying it would unduly withhold the chance of SCV **(Chapter 6)**. Obviously, we need further studies to improve conversion prediction rules and their impact on practices for acute cardioversion. Further, future research should investigate whether cardioversion is needed at all for recent-onset AF and provide evidence for the beneficial role of mHealth in this approach**.**

"The management of atrial fibrillation in the emergency department is not only a sprint to eliminate symptoms and facilitate safe discharge but also the start of a marathon to improve long-term outcomes for patients."
Jeff S. Healey and William F. McIntyre – NEJM 2019

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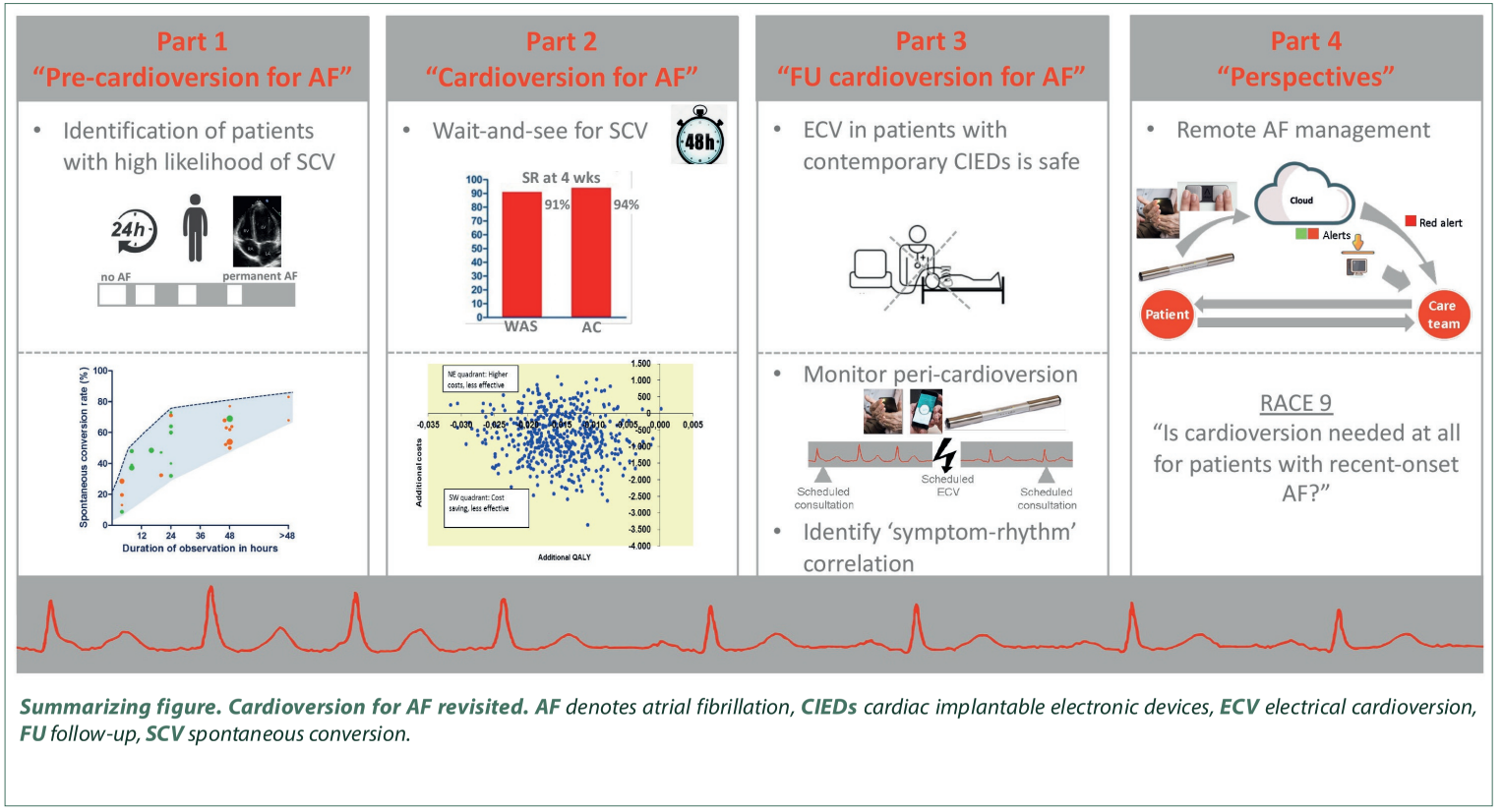
SUMMARY

The central role in this thesis is cardioversion for AF, with as main question whether we should revisit current cardioversion practices for AF in patients with recent-onset AF. But, it also focuses on optimizing the pathway around cardioversion (part 1, 3 and 4). Especially the RACE 7 ACWAS trial has led to a change in the current ESC 2020 guidelines on the management of AF (part 2).
In part I, we showed that spontaneous conversion (SCV) occurs frequently and is mainly depending on the duration of the observation period (range from 9 up to 83% SCVs). SCV occurred more often in patients with first-onset, short-duration AF episodes, lower BMI, absence of underlying heart disease and normal left atrial size, which all may reflect an early phase of AF evolution.

In part 2, the results of the multicenter, randomized trial, RACE 7 ACWAS (Rate Control versus Electrical Cardioversion Trial 7–Acute Cardioversion versus Wait and See) are presented. This trial showed that a wait-and-see approach (with initial rate control to alleviate symptoms and delayed cardioversion only if needed at 48 hours) is non-inferior to early cardioversion (PCV or ECV) in terms of reaching sinus rhythm at four weeks and obviated the need for cardioversion in almost 70% of patients. Over one year, the wait-and-see approach with delayed cardioversion had similar clinical outcome and quality of life compared to early cardioversion for patients with recent-onset AF and there was a trend towards lower costs. This trial has led to a revisit of the cardioversion guidelines for recent-onset AF, which now includes a wait-and-see approach as alternative option for patients with stable recent-onset AF.

In part 3, the management after cardioversion is discussed. Since one of the concerns was that external electrical cardioversion (ECV) may have adverse effects on leads and devices in patients with cardiac implantable electronic devices (CIEDs) we performed a retrospective analysis to evaluate the safety and the need of immediate device interrogation. Our results suggest that external ECV can be performed safely in patients with contemporary CIEDs respecting the recommendations of the ESC guidelines to use biphasic shock waveforms and an anterior-posterior paddle position. Immediate device interrogation seems unnecessary. We also studied the symptom-rhythm correlation in patients with presumed persistent AF planned for elective ECV. The prevalence of a symptom-rhythm correlation around ECV was low and the symptom pattern often changed after ECV. One important limitation of this trial was that the predominantly self-reported symptoms around ECV were obtained retrospectively from patients' medical records and not simultaneously with rhythm information. To improve the identification of a symptom-rhythm correlation a remote heart rate and rhythm infrastructure may be useful which allows simultaneous recording of symptoms and rhythm before and after ECV.

In part 4, the future perspectives and the role of remote heart rate and rhythm monitoring for AF are discussed. The wait-and-see proved to be a good alternative for early cardioversion for patients with recent-onset AF, although the question remains if we should perform a delayed cardioversion at 48 hours, since it is well known that paroxysmal AF can terminate spontaneously up till 7 days and even beyond. Observing the short-term natural course of the disease may improve personalized AF management. A watchful-waiting strategy (rate control to obtain symptom control and only if needed an elective ECV after 4weeks) will investigate the need for cardioversion in patients with recent-onset AF (currently on-going RACE 9 Observe AF trial). To safely implement a watchful-waiting approach, but also to guide a watchful-waiting approach, remote heart rate en rhythm monitoring may have an important role. Currently, no infrastructure is available for remote heart rate and rhythm monitoring which also allows instantaneous treatment decisions. For the RACE 9 Observe AF trial, we developed such infrastructure. The first results of this infrastructure which is based on 1-lead ECG or photoplethysmography (PPG) technology confirmed that this infrastructure is feasible, convenient, broadly accessible and relatively low in costs. Future research should investigate whether cardioversion is needed at all for recent-onset AF and it may provide evidence for the impact of mHealth in this approach.



Summarizing figure. Cardioversion for AF revisited. *AF denotes atrial fibrillation,* ***CIEDs*** *cardiac implantable electronic devices,* ***ECV*** *electrical cardioversion,* ***FU*** *follow-up,* ***SCV*** *spontaneous conversion.*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SAMENVATTING

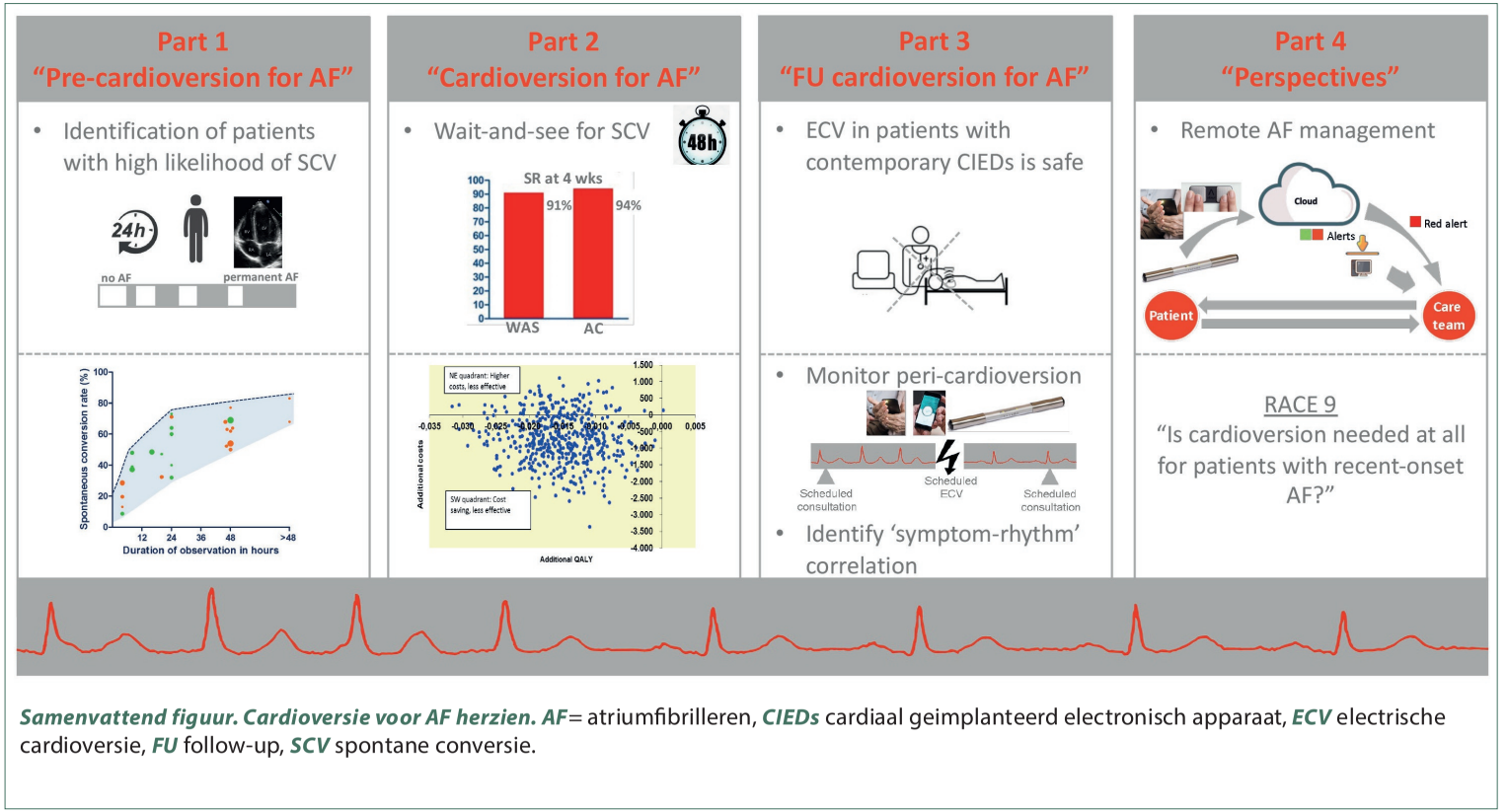
Het centrale onderwerp in dit proefschrift is cardioversie van atriumfibrilleren (AF), met als belangrijkste vraag of we de huidige cardioversie strategie moeten herzien voor patiënten met aanvalsgewijs AF. In deel 2 van dit proefschrift worden de resultaten van de RACE 7 ACWAS studie besproken die bijgedragen hebben aan de aanpassingen van de huidige richtlijnen voor de behandeling AF van de European Society of Cardiology (ESC). Daarnaast wordt in deel 1, 3 en 4 van dit proefschrift ook de optimalisatie van het zorgpad rondom cardioversie besproken.

In deel 1 van dit proefschrift laten we zien dat spontane conversie (SCV) van AF naar sinus ritme vaak voorkomt en met name afhankelijk is van de duur van observatieperiode (range van 9 tot 83% SCV's). Verder zagen we dat SCV vaker voorkomt bij patiënten met een eerste episode van AF; indien er sprake is van een korte duur van de episode; een lager BMI; afwezigheid van onderliggende hartaandoeningen en een normale grootte van het linkeratrium. Factoren die mogelijke allemaal een vroege fase van AF evolutie reflecteren.

In deel 2 van dit proefschrift worden de resultaten van de gerandomiseerde multicenter RACE 7 ACWAS studie (Rate Controle versus Elektrische Cardioversie Trial 7–Acute Cardioversie versus Wait and See) gepresenteerd. Deze studie heeft laten zien dat een wait-and-see aanpak (met initieel rate controle medicatie voor symptoom reductie en indien nodig een cardioversie na 48uur) non-inferieur is ten opzichte van acute cardioversie (farmacologisch of elektrisch) voor het verkrijgen van sinus ritme na 4 weken. Daarnaast was er in 70% van de patiënten in de wait-and-see groep spontaan herstel van sinus ritme en was een cardioversie niet nodig. Deze studie toonde dat ook na een jaar er geen verschil is in klinische uitkomst en kwaliteit van leven tussen de wait-and-see groep en de acute cardioversie groep (hoofdstuk 7). De resultaten van deze studie hebben bijgedragen aan de aanpassingen van de (inter)nationale richtlijnen voor de behandeling van AF, wat nu ook een wait-and-see aanpak als alternatieve optie biedt voor patiënten met stabiel, aanvalsgewijs AF.

In deel 3 van dit proefschrift wordt de behandeling na cardioversie besproken. Een van de vraagstukken die beantwoord wordt is of het veilig is om bij patiënten die een inwendige pacemaker of defibrillator hebben een elektrische cardioversie uit te voeren en of een doormeting van het apparaat nadien noodzakelijk is. De resultaten van onze retrospectieve analyse gepresenteerd in hoofdstuk 8 suggereren dat het uitvoeren van een elektrische cardioversie bij patiënten met een inwendige pacemaker of defibrillator veilig kan, met inachtneming van de aanbevolen veiligheids-maatregelen zoals voor-achterwaartse positie van de electroden en bifasische schok toediening. In deze studie werden geen afwijkingen gevonden bij directe doormeting van de pacemaker of defibrillator na cardioversie, en om deze reden wordt verondersteld dat een directe doormeting niet nodig is. In hoofdstuk 9 wordt de relatie tussen symptomen en AF rondom een elektrische cardioversie onderzocht. Vaak is het moeilijk om te achterhalen of iemand symptomen heeft door AF (symptoom-ritme correlatie) of dat de symptomen veroorzaakt worden door de co-morbiditeiten die vaak aanwezig zijn bij patiënten met AF. In deze retrospectieve analyse zijn de symptomen beoordeeld vóór elektrische cardioversie en de symptomen een maand na elektrische cardioversie. Na een maand had reeds 64% van de patiënten recidief AF. Wat opviel in deze studie is dat op basis van enkel retrospectieve symptoom-ritme analyse, het moeilijk is om te evalueren of er een symptoom-ritme correlatie is. De bevindingen van deze studie waren dat een symptoom-ritme correlatie niet vaak gevonden werd en dat symptomen vaak dynamisch zijn over de tijd. Omdat deze studie op retrospectieve data gebaseerd is, is enkel het meest voorkomende symptoom meegenomen in de analyse, en dit kan invloed hebben op de dynamiek van symptomen die we zien. Daarnaast is de evaluatie van symptomen niet gelijktijdig met het ritme gedaan, en ook dit kan van invloed zijn op de symptoom-ritme correlatie. Om de evaluatie van de symptoom-ritme correlatie te verbeteren zou een gelijktijdige beoordeling van symptomen en ritme (digitaal) kunnen bijdragen.

In deel 4 van dit proefschrift worden de toekomst perspectieven besproken met ook aandacht voor de opkomst van digitale gezondheidszorg. In dit proefschrift hebben we laten zien dat een wait-and-see aanpak een goed alternatief kan zijn voor patiënten met stabiel, aanvalsgewijs AF. In 30% van de patiënten in de wait-and-see groep wordt echter na 48uur nog een cardioversie uitgevoerd. De vraag blijft echter of dit nodig is, aangezien bekend is dat aanvalsgewijs AF spontaan termineert en dit kan ook na 48 uur nog optreden. Het wachten op spontane conversie heeft een aantal voordelen zoals het voorkomen van onnodige behandeling, en het observeren van spontane conversie geeft ook belangrijke informatie voor toekomstige behandeling. Om deze reden willen we in de RACE 9 Observe AF studie patiënten met aanvalsgewijs AF, die zich presenteren op de Eerste Hart Hulp behandelen met uitsluitend rate controle medicatie en gedurende 4 weken evalueren of het ritme spontaan herstelt. Deze strategie wordt 'watchful-waiting' genoemd. Om dit veilig te implementeren wordt in deze studie gebruik gemaakt van controle op afstand van hartritme en hartfrequentie. Deze digitale infrastructuur was nog niet beschikbaar en is voor deze studie ontwikkeld. De eerste resultaten van deze infrastructuur voor op afstand beoordeling van hart ritme en frequentie staan in hoofdstukken 10-12. Er wordt gebruik gemaakt van een smartphone die met behulp van de camera van de telefoon op basis van fotoplethysmografie (PPG) hartritme en hartfrequentie kan beoordelen. De eerste resultaten gepresenteerd in dit proefschrift tonen dat deze infrastructuur uitvoerbaar is, makkelijk in gebruik, breed toegankelijk en laag in kosten. Toekomstig onderzoek moet uitwijzen of cardioversie voor stabiel aanvalsgewijs AF überhaupt nog nodig is en of de digitale infrastructuur voor op afstand hartritme en hartfrequentie te beoordelen hierbij behulpzaam kan zijn.



Samenvattend figuur. Cardioversie voor AF herzien. AF= atriumfibrilleren, ***CIEDs*** cardiaal geimplanteerd electronisch apparaat, ***ECV*** electrische cardioversie, ***FU*** follow-up, ***SCV*** spontane conversie.

SCIENTIFIC AND SOCIETAL IMPACT

Atrial fibrillation (AF) is the most commonly encountered arrhythmia in adults worldwide[1] and causes a significant health care burden. [2] In the Netherlands over 360.000 people are diagnosed with AF, and each day 94 patients present to the hospital with AF.[3] The current comprehensive management approach for AF focuses on alleviation of symptoms and prevention of serious adverse events.[1] To alleviate symptoms rate or rhythm control treatment can be initiated or adapted. A rate control strategy primarily focuses on symptom relief by reducing the ventricular heart rate with rate control drugs, while rhythm control can be achieved by pharmacological (PCV) or electrical cardioversion (ECV).[1] The central question in this thesis is whether the cardioversion strategy should be revisited. One of the most important conclusions concerning this question derives from the RACE 7 ACWAS trial **(Chapter 4)**. This trial showed that a wait-and-see approach (with initial rate control to alleviate symptoms and delayed cardioversion only if needed at 48 hours) is non-inferior to early cardioversion (PCV or ECV) in terms of reaching sinus rhythm at four weeks and obviated the need for cardioversion in almost 70% of patients. This trial has a major scientific impact since it has led to a revisit of the cardioversion guidelines for recent-onset AF, which now includes a wait-and-see approach as alternative option for patients with stable recent-onset AF. Besides the scientific impact of this trial, it has several societal aspects. First of all, in almost 70% of patients a cardioversion -along with its potential complications - may be avoided. Secondly, the time spent in the often overcrowded emergency departments may be reduced. Thirdly, patients may have the experience that their arrhythmia terminated by itself, which may broaden their insight into treatment options and may improve self-management. Fourthly, although not statistically significant there is a trend towards lower costs.

Besides this, also the first part of the thesis, which focuses on identifying patients with a high likelihood of spontaneous conversion, has a societal impact. Since, identification of patients in an early stage could prevent hospital visits (and thereby healthcare costs), and may improve self-management. In the last part of the thesis the future perspectives and the role of remote heart rate and rhythm monitoring for AF are discussed. The exact scientific and societal impact will be investigated in the on-going trials (RACE 9 Observe-AF; TeleCheck-AF) although there are some preliminary results. In recent years many mHealth solutions have become available for heart rate and rhythm assessment, but no infrastructure was available for remote heart rate and rhythm monitoring which also allows instantaneous treatment decisions. We developed such mHealth infrastructure which is based on 1-lead ECG or photoplethysmography (PPG) technology, and the first results **(Chapter 10)** confirmed that this infrastructure is feasible, convenient to use, broadly accessible and relatively low in costs. In the on-going RACE 9 Observe AF trial we are combining this infrastructure with a new watchful-waiting approach for patients with recent-onset AF. This watchful-waiting strategy (rate control to obtain symptom control and only if needed an elective ECV after 4 weeks) will evaluate the need for cardioversion in patients with recent-onset AF. The hypothesis is that the implementation of this watchful-waiting strategy managed by remote rhythm monitoring for recent-onset AF will obviate the need for cardioversion, improve resource utilization in emergency departments, and reduce costs. And since AF is a chronic disease, this remote mHealth infrastructure as well as the watchful-waiting strategy may also improve patient education about the recurrent and transient nature of AF. Also, having the opportunity to communicate 'on-line' with their care team may reduce patients' anxiety and broaden their insight into treatment options. The exact scientific and societal impact will be investigated in the RACE 9 Observe AF trial and the TeleCheck-AF project.

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DANKWOORD

Misschien wel het meest belangrijke hoofdstuk van mijn proefschrift, want dit proefschrift was niet tot stand gekomen zonder de steun van velen. Op deze plaats wil ik dan ook iedereen bedanken die heeft bijgedragen aan mijn proefschrift. Een speciale dank ook naar alle betrokkenen van de RACE 7 ACWAS studie, zonder jullie hadden we dit prachtige resultaat niet kunnen bereiken!

Ook al ben ik van mening dat niets onmogelijk is, toch is het zeer uitdagend om in dit hoofdstuk iedereen te benoemen die heeft bijgedragen aan dit proefschrift. Zoals jullie wellicht al gezien hebben, heb ik voor een iets andere opzet gekozen, en zal ik slechts een aantal hier met naam benoemen.

Allereerst mijn promotieteam. Mijn promotor, prof. Dr. H.J.G.M. Crijns, wat heb ik vele lessen van u mogen leren. Niet alleen op gebied van wetenschap, maar zeker ook als klinische dokter en persoon. Ik zal altijd met plezier terugdenken aan het schrijven van de RACE 7 ACWAS en RACE 4 studie. De urenlange schrijfsessies samen met prof. Dr. Tijssen, de eindeloze syntax analyses samen met Petra en de vaak uitdagende deadlines, zijn de grondslag van dit proefschrift. Het was een eer om dit traject onder uw begeleiding te mogen doorlopen. Bedankt voor de kansen die u mij heeft gegeven en het gestelde vertrouwen!

De co-promotores. Als eerste Dr. J.G.L.M. Luermans, beste Justin, ondanks je drukke agenda maakte je altijd tijd vrij. Met veel geduld, perfectionisme en enorm enthousiasme begeleidde je mij door mijn PhD, superviseerde je de AF-poli en heb ik nadien veel van je mogen leren als assistent in de kliniek. Hopelijk kunnen we komende jaren nog veel samenwerken zowel op het gebied van onderzoek als in de kliniek!

Dr. D.K. Linz, beste Dominik, je bent pas in een later stadium aangesloten bij mijn promotieteam maar met je aanstekelijke enthousiasme en geniale onderzoeksideeën hebben we in mijn laatste jaar nog een heel nieuw deel aan mijn proefschrift toegevoegd. En ik weet zeker dat dit nog maar het begin is!

Beste leden van de beoordelingscommissie en corona, bedankt voor de kritische beoordeling van mijn proefschrift en jullie bereidheid om aanwezig te zijn tijdens mijn verdediging. Dear members of the assessment committee and corona, thank you for assessing my thesis and defence.

Tijdens mijn verdediging word ik bijgestaan door de twee personen die mij het hele traject bijgestaan hebben, drs. Y.J.M. van Cauteren en dr. E.A.M.P. Dudink, mijn paranimfen. Allereerst Yvonne, wat heb jij me al ontelbare keren uit de brand geholpen, ik ben jou veel dank verschuldigd. Zonder enige aarzeling sta je altijd klaar voor anderen, dat siert je! Ik kijk ernaar uit om komende jaren met je als AIOS in de kliniek samen te werken, en hopelijk volgen er nog veel leuke uitjes, skitripjes en vele kilometers op de fiets samen. Elton, jou opvolgen zorgde er meteen voor dat de lat heel hoog werd gelegd. Ik mocht onder andere de RACE 7 ACWAS van jou overnemen; dit zorgde ervoor dat ik een vliegende start kon maken met mijn PhD. Meteen starten met een multicenter studie voelde als een sprong in het diepe, en zeker waren er de nodige obstakels en uitdagingen die hier bij horen, maar ik kon altijd laagdrempelig bij je terecht met al mijn vragen, en wat een mooi resultaat is het geworden! We hebben nog een aantal projecten lopen voor komende jaren, en ik weet zeker dat ook deze nog mooie resultaten gaan brengen.

Lieve collega's, vrienden en familie, samen met jullie heb ik mogen ervaren dat een promotietraject een unieke ervaring is waar ik afgelopen jaren met veel plezier aan heb gewerkt. Jullie zorgden voor een team waar ik op kon rekenen. Ook al was ik bij deadlines niet altijd te genieten en had ik weinig aandacht voor andere zaken, toch waren jullie er altijd voor mij! Met jullie steun en toeverlaat heb ik dit proefschrift kunnen afronden. Heel veel dank!

ABOUT THE AUTHOR

Nikki Agnes Harry Anne Pluymaekers
Geboren op 31 oktober 1989 te Maastricht

After graduating the Athenaeum and achieving her propaedeutic examination in Law, she started in 2010 with her medical training at the Faculty of Health, Medicine and Life Sciences at the Maastricht University. In 2014 she went to Italy for a research internship at the department of internal medicine at the Papa Giovanni XXIII hospital in Bergamo. Under supervision of prof. dr. Brucato she developed her interest in research. After graduating as a Medical Doctor, she joined the research group of prof. dr. Crijns in 2016 at the department of Cardiology at the Maastricht University Medical Center and started with her PhD. The results are presented in this thesis. Currently, Nikki is working as a cardiologist in training at the Maastricht University Medical Center.

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Jul 2015 Pericarditis in children and adolescents: etiology, characteristics, therapies, and outcomes. A multicenter cohort study. (Poster presentation, ISCOMS congress, Groningen, The Netherlands.

Jun 2017 P1498 External electrical cardioversion in patients with cardiac implantable electronic devices: is it safe and is immediate device interrogation necessary? (Poster presentation, Europace congress, Vienna)

Mar 2018 P456 External electrical cardioversion in patients with cardiac implantable electronic devices: is it safe and is immediate device interrogation necessary? (Poster presentation, EHRA congress, Barcelona, Spain)

Aug 2018 Abstract 81803 - Clinical determinants of spontaneous conversion to sinus rhythm in patients presenting at the emergency department with atrial fibrillation. (Poster presentation, ESC congress, Munich, Germany)

Oct 2018 Management of idiopathic recurrent pericarditis during pregnancy.(Participation in the Young Investigator Award during 15th Annual Conference of the ESC Working Group on Myocardial and pericardial diseases)

Nov 2018 Clinical Determinants of Early Spontaneous Conversion to Sinus Rhythm in Patients Presenting at the Emergency Department with Atrial Fibrillation. (Oral presentation The Netherlands Society of Cardiology Congress)

Apr 2019 Wait-and-see versus acute cardioversion in recent-onset atrial fibrillation. (Oral presentation The Netherlands Society of Cardiology Congress, award best presenter session arrhythmias)

Nov 2019 6e WCN research award 3e plaats. WCN-congress 2019. (Early or delayed cardioversion in recent-onset AF).

Mar 2020 One year clinical outcome and cost-effectiveness of delayed versus early cardioversion in recent-onset atrial fibrillation. Results from the RACE 7 ACWAS trial. (Accepted as late breaking clinical trial presentation, due to COVID-19 congress cancelled)

Aug 2021 ECG challenges from smartwatch recordings. Invited presentation ESC Congress 2021 –The Digital Experience.


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