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Transtelephonic ECG Monitoring to Guide Outpatient Antiarrhythmic Drug Therapy in Patients With Non-Permanent Atrial Fibrillation: Efficacy and Safety From a Single-Center Experience

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Abstract

Initiation of antiarrhythmic drug therapy (AADx) for atrial fibrillation (AF) on an outpatient basis requires intensive ECG monitoring in order to assess antiarrhythmic efficacy as well as ECG signals of potential proarrhythmia. Dronedarone (DRO) reduces cardiovascular endpoints in AF patients fulfilling criteria of the ATHENA trial [1]. In the present study transtelephonic ECG monitoring was used to guide initiation of AADx in AF patients fulfilling the ATHENA criteria.

In 19 consecutive patients (37% female; age 65+10 years; LVEF 62+7%; mean CHA2DS2-VASc score 2.9 + 1.6 (median=2), with symptomatic non-permanent AF and additional cardiovascular risk factors, DRO was prescribed as AADx of first choice. Initiation of therapy and follow-up were monitored by transtelephonic ECG recordings (VITAPHONE™100 IR; Vitaphone GmbH; Germany). In patients with persistent AF, electrical cardioversion was performed on an outpatient basis when DRO was started. Patients were followed for changes in QT intervals as well as AF recurrency. ECGs were transmitted according to a scheduled FU form as well as any time in case of pts symptoms.

Patients in whom DRO did not prevent AF recurrence were switched to alternative AADx, or to pulmonary vein isolation (PVI), respectively. At the end of long-term follow-up, DRO alone was successful in preventing AF recurrence in 5 of 19 patients (26%). When pts who responded to AADx of second or third choice or who underwent PVI were included, SR could be maintained in 17/19 pts (89%). No patient required discontinuation of AADx due to ventricular depolarization abnormalities, symptomatic bradycardia or pathologic QT prolongation.

In conclusion, transtelephonic ECG transmission is useful for close rhythm monitoring during initiation and follow-up of AADx, also during change from DRO to other AADx. DRO was effective to prevent AF recurrence in 26% of patients during a mean long-term follow-up of more than 30 months – which is well in line with data from the literature.

Introduction

Antiarrhythmic drug therapy (AADx) for restoration and/or maintenance of sinus rhythm remains a mainstay of treatment in highly symptomatic patients with non-permanent atrial fibrillation (AF), also in the era of interventional therapy of atrial fibrillation by means of catheter ablation [2-5]. However, AADx has potential pro-arrhythmic effects and its initiation requires intense ECG monitoring, particularly during the initial phase of treatment. Furthermore, pharmacologic therapy of non-permanent AF is characterized by a limited clinical long-term efficacy [3,6,7] and patients on AADx who were highly symptomatic prior to treatment may turn asymptomatic even in case of AF recurrence while on AADx [8]. Prolonged rhythm monitoring may thus be helpful in identifying patients with asymptomatic AF in whom modification of therapeutic strategies may be required.

Key Words

Atrial fibrillation, Transtelephonic ECG monitoring, Antiarrhythmic drug therapy.

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Recently, the multi-class AAD dronedarone has been added to the limited number of pharmacological armentarium of AF treatment. This drug is particularly an option in patients with additional cardiovascular risk factors such as atherosclerosis or hypertension [1]. The aim of the present study was to investigate the feasibility and clinical utility of guiding AADx by regular transtelephonic ECG monitoring in patients with non-permanent AF and additional risk factors who did not opt for pulmonary vein isolation (PVI) and in whom Dronedarone was prescribed as first line treatment.

Methods

In this prospective single-centre feasibility study at a cardiology outpatient office, consecutive patients with a history of symptomatic non-permanent AF and de-novo prescription of Dronedarone were offered to have transtelephonic ECG monitoring by means of a portable easy-to-use device instead of frequent in-office ECG registration during initiation and follow-up of AADx. Patients received a transtelephonic device (VITAPHONE 100 IR™, Vitaphone, Germany; [Figure 1] [Table 1]) on the day when Dronedarone was prescribed. The device can store a maximum of 3 episodes of a 30-second 1-lead ECG. After 3 registrations the

Figure 1: Transtelephonic ECG device used in the study (Vitaphone, Germany)

patients had to transmit the ECG data by telephone, after which the storage was cleared and the device ready for new ECG recordings. After transmission, a pdf with the ECG strip was generated and automatically sent to the investigator by e-mail. In order to ensure appropriate use of the device, the first ECG was registered immediately in-office. Also, the patient was asked to send additional 1 or2 ECGs from their home the same day and before the first dose of dronedarone. ECGs were analyzed with regard to the nature of rhythm, heart rate, and changes in QT interval, respectively. After start of AADx, patients were asked to record and transmit ECGs according to a pre-specified transmission schedule [Table 2]. Written informed consent was obtained from all patient with regard to the above mentioned study procedure. In particular, patients agreed that their ECG data were processed transtelephonically with the ECG tracings generated automatically and sent as pdf file per e-mail to the investigator. All electronic transmission and processing of ECG data were performed anonymously with the ECG tracing linked to the serial number of the ECG device.

Table 1: Technical data of the Tele-ECG device (VITAPHONE IR100, Vitaphone GmbH, Germany)

Leads	1 (bipolar)
A/D resolution	12 Bit
Frequency range	0.5 – 40 Hz
Max number of stored events	3
Duration of ECG event	30 sec

Table 2: ECG transmission schedule after initiation of AADx

Baseline ECG protocol		
Day 1-2	2 ECG/day	Additional ECG any time, e.g. in case of symptoms
Day 3-14	1 ECG/day	Additional ECG any time, e.g. in case of symptoms
Week 3-4	1 ECG / 2 days	Additional ECG any time, e.g. in case of symptoms
Beyond week 4	2 ECGs / week	Additional ECG any time, e.g. in case of symptoms
Beyond month 3	1 ECG / 1-2 weeks	Additional ECG any time, e.g. in case of symptoms
Additional recordings		
Change of AADx (see protocol above)		Additional ECG any time, e.g. in case of symptoms

(AADx=antiarrhythmic drug therapy; ECG=electrocardiogram)

Patients were followed for at least 6 months. Analysis of transtelephonic ECG recordings was performed as follows: number of episodes; quality of episodes; Heart rate and rhythm (SR vs AF) as from the electronic file. QT/QTc were measured from the ECG printouts with standard methods. The time of first AF recurrence was recorded. Changes in AADx as well as the total number of AADx used were recorded. The type of heart rhythm was recorded at each treatment step.

Data were analyzed using SPSS Vs 14. Descriptive statistical analysis was used. All patients still in SR at the time of data analysis were considered as Dronedarone responder. All patients in SR irrespective of the AAD used at the end of follow-up were defined as AAD responder.

Table 3: Patient characteristics

	N = 19
Females	7 (3177%)
Age (years)	65 + 10
LVEF (%)	62 + 7
Hypertension	17 (89%)
CAD	5 (26%)
No structural HD	2 (11%)
Previous AAD	1 (5 %)
Median CHADSVaSC (mean)	2 (2.9 + 1.6)

(AAD= antiarrhythmic drug; CAD=coronary artery disease; HD=heart disease; LVEF=left ventricular ejection fraction)

Results

Patient population

Between August 2011 and September 2012 a total of 19 patients were included in the study. Seven patients (37%) were female. Age averaged 65+10 years; mean LVEF was 62+7%. Median CHA2DS2-VASc score was 2 with a mean of 2.9 + 1.6. Mean follow-up was 36 + 21 months. Whereas the majority of patients had paroxysmal AF at the time of inclusion, 8 patients had persistent AF and underwent electrical cardioversion at the time of initiation of dronedarone therapy and inclusion into the study. All patients had at least one cardiovascular risk factor, most of them hypertension. [Table 3] depicts the clinical characteristics of the patient population.

Data collection and long-term follow-up

As already outlined above, patients were instructed to regularly transmit ECGs according to the protocol depicted in [Table 4].

Table 4: Follow-up and endpoints

Mean FU (months)	35 + 21
Sinusrhythm@ 6 months	16 (84 %)
Sinusrhythm@ 12 months	14 (74 %)
Sinusrhythm@ 24 months	11 (58 %)
No of AAD per patient during FU	
1 AAD (Dronedaron only)	6 (43 %)
2nd AAD	13(36 %)
3rd AAD	5 (14 %)
Subsequent PVI	6 (7 %)

(AAD=antiarrhythmic drug; FU=follow-up; PVI = pulmonary vein isolation)

Long-term follow-up was initiated. Only 2 patients decided to return their monitoring device prematurely; they were censored at the date of the last diagnostic ECG recording.

A total of 5258 ECGs were collected over time. These were 1-lead recordings of 30 sec duration. Patients showed a high adherence to the protocol and the quality of ECG recordings was high. Less than 5% of ECG recordings were not readable due to artifacts. Thus, nearly all ECG recordings were analyzable with respect to the underlying rhythm, conduction disturbances, and potential changes in repolarization. Each ECG was compared to the respective

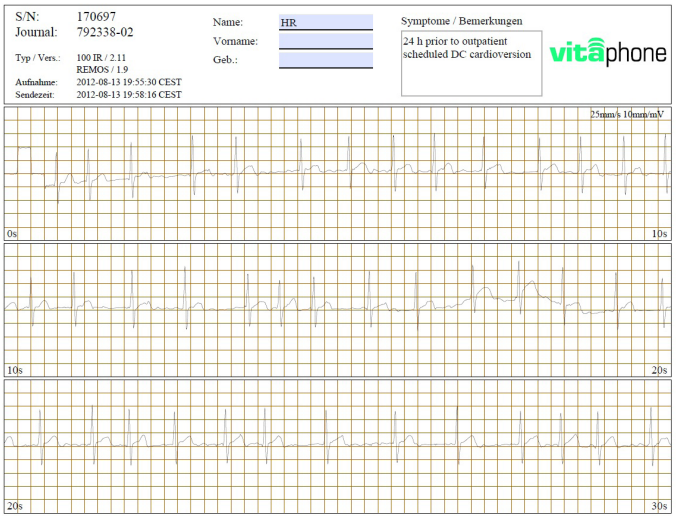

Figure 2A: Transtelephonic ECG in a patient with persistant AF prior to cardioversion and initiation of AADx with dronedarone

previous ECG. In case of changes – i.e. recurrence of AF – the patient was contacted and asked to increase the frequency of ECG transmission. In case of persistence of AF the patient was seen in the arrhythmia clinic to evaluate change in AAD therapy and / or to plan a cardioversion procedure. [Figure 2A+B] depict examples of transtelephonic ECG transmission in a patient prior to and after cardioversion of AF.

The mean duration of follow-up on regular ECG transmission was 36 + 21 months. A total of 5258 ECGs (28-792) were transmitted from 19 patients. The shortest follow-up was 3 months, the longest was 60 months. Fifteen patients (79 %) were followed 12 months or

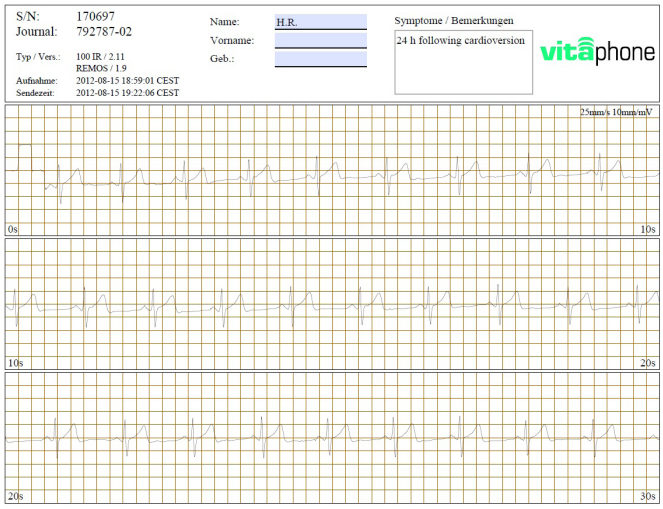

Figure 2B: Transtelephonic ECG on day 2 following cardioversion and on treatment with dronedarone

longer, 13 patients (68 %) sent regular ECG recordings for longer than 24 months, and eight patients (42 %) for 4 years or longer.

Monitoring results of antiarrhythmic efficacy

All patients could be guided safely and efficiently by transtelephonic ECG monitoring. Only one patient required an additional teaching with respect to appropriate use of the device. [Figure 3] depicts the efficacy result of AADx according to the findings of the transmitted ECG recordings. Therapeutic efficacy was defined as documentation of persistent sinus rhythm. As expected, a majority of patient had to change antiarrhythmic drug therapy over time, such as a 2nd choice or 3rd choice AAD or switching to PVI. The reason for changing antiarrhythmic therapy was either persistent AF, or no change or even an increase in paroxysmal AF episodes. Of the 13 patients who had to switch to a 2nd AAD, 11 (85%) did so within the first 10 months, 2 patients switched from dronedarone to another drug beyond 20 months of initially efficient treatment. Seven patients remained on dronedarone beyond 1 year of treatment. This 37% one-year efficacy rate is well in line with those described elsewhere [3,9]. Four patients (21 %) were still taking dronedarone after the end of the study (with

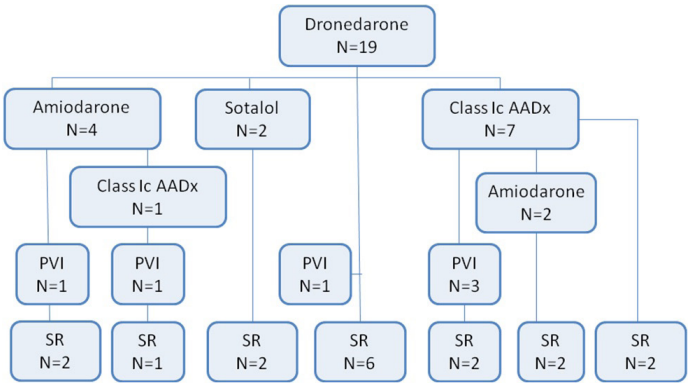

Figure 3: Flowchart: Treatment with AADx, including change to 2nd and 3rd choice drug, and catheter ablation, respectively. At the end of follow-up only 2/19 patients (11 %)had developed permanent AF.

(AADx= antiarrhythmic drug therapy; PVI= pulmonary vein isolation; SR = sinus rhythm)

follow-up times of 27, 38, 47, and 53 months). Regarding the 2nd choice AADx, these were Class Ic drugs in 7, amiodarone in 4, and sotalol in 2 patients. Of these, 2 class Ic patients were prescribed amiodarone as 3rd choice drug, 2 amiodarone patients were switched to class Ic drugs, and only 1 patient had a change within the AADx class Ic (from propafenone to flecainide). The main reason for stopping dronedarone was antiarrhythmic inefficacy (i.e. AF recurrence) in 11 patients. QTc-interval averaged 428 + 18 ms during the first TTEM recording, which was not different from QTc assessed from the last 12-lead ECG. No patient had a QTc > 470 ms at entry , or > 500 ms after 1 months on dronedarone. The number of PVC or PAC was not analysed since the recordings were too short for that purpose.

One patient developed bradycardia and diastolic heart failure, and underwent pacemaker implantation and subsequent change of AADx to amiodarone. As depicted in [Figure 3], six patients underwent PVI during follow-up, all due to symptomatic recurrent AF during AADx. All of these continued using the ECG monitoring device and four of them remained free from symptomatic AF during follow-up of the study.

Discussion

Initiation of AADx in AF patients requires regular ECG monitoring [1]. Recently, several approaches of screening for or rhythm monitoring in AF have been proposed, ranging from symptom-guided event recording to continuous monitoring through implantable devices [8,10-15].

The present study is the first to investigate a systematic protocol for patient-activated transtelephonic ECG monitoring (TTEM) in patients with symptomatic non-permanent atrial fibrillation undergoing de-novo AADx with dronedarone as first-line / de-novo medication. The results of the study demonstrate that TTEM is a feasible and effective means of rhythm monitoring in patients with non-permanent AF. The quality of recordings was extremely high with only 4 % of recordings being not diagnostic regarding the underlying rhythm (largely due to artifacts). Also, adherence to the prespecified protocol was high. Only 2 patients stopped rhythm recording prematurely for no specified reason. The second finding of the study is that – using a stepwise therapeutic approach – nearly 90% of patients were in persistent SR at the end of follow-up. In 26% of patients, dronedarone was effective throughout the very long follow-up period in maintaining SR; the efficacy rate during the first year was 37%. This proportion is well in line with efficacy data for dronedarone found in other clinical trials. For example, the ADONIS/EURIDIS programme demonstrated a 1-year efficacy rate of dronedarone of 30% [9]. The study by Freemantle depicts efficacy rates for different antiarrhythmic drugs and found similar antiarrhythmic efficacy rates [3]. Furthermore, TTEM is effective in observing ventricular repolarization changes in patients under AADx for non-permanent AF. In no patient, excessive QT prolongation was seen. TTEM thus proved to be an effective safety tool for guiding AADx.

TTEM by simple-to use Tele-ECG card has been described previously and has been found to be effective in documenting the underlying rhythm in patients with clinical suspicion of a cardiac arrhythmia [13]. So far most studies have addressed the value of such devices with regard to diagnosis making rather than assessing safety and efficacy of a specific AADx target to AF. The method of extended TTEM used in the present study has been described elsewhere. For example, in a study of Busch and colleagues, this system was used to identify AF patients in a population-based setting. The incidence of newly diagnosed AF was 2.6% as compared with only 1.3% with normal ECG registration [15]. To our knowledge, the present study is the first to use regular consecutive Tele-ECG registrations in order to monitor AADx safety and efficacy in AF. The quality of data was good in the present study. Gosciniak et al used TTEM to monitor heart rhythm after successful surgical ablation of AF. The quality of ECG signal was comparable to that in the present study. TTEM proved to be safe in rhythm follow-up in that patient cohort [12].

In summary, TTEM proved to be safe and efficient to guide patients even through a long-term follow-up after cardioversion of AF, including monitoring of subsequent changes of therapeutic strategy of AF treatment over time. Patient adherence was excellent. Complications did not occur.

The present study thus proves that TTEM may be helpful in improving patient care during initiation and follow-up of antiarrhythmic drug therapy for atrial fibrillation. It can be expected that automatic ECG monitoring, e.g. by implantable monitoring devices may further improve patient management following pharmacologic or interventional rhythm control strategies of atrial fibrillation [14].

Limitation

The present study has several limitations. One is the relatively small number of patients studied. This relates to the fact that these were highly selected patients with non-permanent AF in whom AADx was preferred over PVI as primary treatment choice. There is limited number of such patients in an era where PVI is considered the primary option in the majority of patients with non-permanent AF. Furthermore, patient-activated transtelephonic ECG monitoring is a clinical tool that – although being introduced for years – is yet far from being general clinical practice in many countries. Therefore the present study was designed as a feasibility and hypothesis-generating study. A larger trial comparing transtelephonic monitoring with regular care in patients with non-permanent atrial fibrillation is urgently warranted. Also, we did not test how long and by how many ECG transmissions patients should be followed optimally. We aimed to collect as much ECGs as possible in this feasibility study, however the use of shorter follow-up periods and different numbers of transmission may be sufficient. Another limitation is related to the fact that patients transmitted ECGs at predefined time-points, or when they felt symptoms. This probably caused underestimation of potential asymptomatic AF episodes. Such underestimation is however immanent to any patient-based event recording.

The inclusion of patients only with de-novo Dronedarone AADx was chosen in order to have a relatively "homogenous" patient population. The clinical efficacy of Dronedarone in this predefined population can be seen as secondary aspect of the study; the results are well in line with efficacy data for dronedarone from previous

clinical trials. In this context, another limitation relates to the fact, that QT- an QTc-measurement from transtelephonic 1-lead ECG strip carries the risk of inaccuracy. In all 19 patients, we compared the QTc from the first TTEM recording with the QTc from the standard resting 12-lead ECG before starting AADx. QTc was measured from all transmitted ECGs. We observed intraindividual variation in QRS morphology since patients sometimes used different positions for placement of the ECG device which made comparisons of QTc measurements difficult. However, the QTc did not exceed 500 ms in any patient.

The present study does not include patient questionnaires or economic analysis, since this was beyond the scope of this feasibility study. However, documentation of patient history during follow-up visits indicated a favorable acceptance and satisfaction with the ECG system. The cost-saving potentials of TTEM over regular care need to be assessed in a larger study in which both follow-up options are compared.

Ethics

The present study was conducted according to the Declaration of Helsinki. Informed consent was obtained from all subjects.

Conclusions

Transtelephonic ECG transmission is useful for close rhythm monitoring during initiation and follow-up of AADx, also during change from DRO to other AADx. DRO was effective to prevent AF recurrence in 26% of patients during a mean long-term follow-up of more than 30 months – which is well in line with data from the literature.

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