Principles and Practice of Clinical Research
A Global Journal in Clinical Research

PPCR
ISSN: 2378-1890

Fast approach by a multidisciplinary specialized team for atrial fibrilation compared to the standard of care in the emergency department - FAST-AF

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Received January 15, 2017; accepted May 23, 2018; published July 25, 2018.

Abstract:

Introduction: *Atrial fibrillation (AF) is the most common sustained cardiac rhythm abnormality. AF treatment is provided by either cardiologists or non-cardiologists and is based on the prevention of thromboembolic events and on heart rate control or rhythm control. There is evidence that AF management by specialists leads to improved patient outcomes. Moreover, management of complex cardiac arrhythmias by a specialized team has been considered helpful by an overwhelming majority of practicing physicians. Therefore, we designed a multidisciplinary team - Fast Approach by a Specialized Team for Atrial Fibrillation (FAST-AF) - to evaluate the treatment effectiveness of a specialized arrhythmia team compared to the standard of care in the management of patients with new-onset AF presenting in the emergency department (ED).*

Methods: *We propose an open-label, single-center, randomized, parallel group, superiority trial in a university hospital during a period of 36 months. 294 patients with new-onset AF presenting in the ED will be randomized in a 1:1 ratio to FAST-AF or standard of care. The primary outcome will be time to discharge from the beginning of the intervention. Secondary outcomes will be time to heart rate/rhythm control, compliance to anticoagulation after discharge, readmission rates, quality of life assessment (AFEQT) and hospitalization costs. For the primary analysis, an intention-to-treat (ITT) time to event (TTE) analysis will be conducted. The trial will be prospectively registered at ClinicalTrials.gov.*

Conclusion: *AF is a prevalent disease that causes several complications and morbidity. The heterogeneity of medical criteria, the lack of knowledge of international guidelines and inadequate adherence to treatment may compromise therapeutic success. This study design is readily replicable, given its simplicity and feasibility. If the study show promising results of FAST-AF intervention, future studies can be conducted to assess cost reduction and specialized consultation by virtual meeting platforms.*

Keywords: *Atrial fibrillation, new-onset, multidisciplinary team, treatment, emergency department.*

DOI: http://dx.doi.org/10.21801/ppcrj.2018.41.4

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac rhythm abnormality. In 2010, its prevalence in the United States ranged approximately from 2.7 to 6.1 million, and in 2050 it is expected to increase twofold (Go et al., 2014). Regarding AF cases, 3.3 to 10% occurs during admissions to the emergency department (ED), with a mortality risk of 4, 6, and 11% in the follow-up at 30, 90, and 365 days, respectively (Atzema, Lam, Young, & Kester-Greene, 2013; Russo et al., 2013). As aging is a risk factor to develop AF, the number of patients seen in the ED with AF is projected to markedly increase in the upcoming years; in 2006 there were 564,000 ED visits in the United States with primary diagnosis of atrial fibrillation, 88% more than in 1994 (Atzema et al., 2013).

AF major concerns are related to its complications; for instance, 20% of all strokes, result from AF, increasing the in-hospital mortality which has been calculated at 2.1%, 20 times greater than the overall mortality rate in hospitalized patients without AF (Russo et al., 2013). For these reasons, the management of AF is challenging and should be prompt, optimal, and extended to improve the care and prognosis of patients.

Recently, the European Heart Rhythm Association conducted a survey to provide an insight into the role of an integrated, multidisciplinary team, known as "Arrhythmia Team" for the management of patients with cardiac arrhythmias. Results showed that 95% of respondents considered it helpful and 79% agreed that it should be implemented (Fumagalli et al., 2016). Also, a nurse-led AF clinic showed that providing integrated, extended care improved guidelines adherence by increasing patient self-awareness through education was superior to usual care provided by a cardiologist regarding cardiovascular hospitalizations and cardiovascular mortality, as well as cost-effectiveness and quality of life of patients (Hendriks et al., 2012; Hendriks, Tomini, Van Asselt, Crijns, & Vrijhoef, 2013). Although a specialized arrhythmia team for AF treatment could improve the outcomes in outpatient clinics, there are no studies that assess its impact in an ED setting. Therefore, we propose an open-label randomized clinical trial to evaluate the efficacy of emergency AF treatment provided by a multidisciplinary team - Fast Approach by a multidisciplinary Specialized Team for Atrial Fibrillation (FAST-AF) -compared to standard of care. Our primary hypothesis is that the FAST-AF will benefit patients and emergency health care services in newly onset AF.

MATERIALS AND METHODS

The study design is a single center, open-label, randomized clinical trial, to compare similar guidelines and treatment between two organized different teams (FAST-AF vs Standard care) in order to determine which is the most effective in patients new-onset AF at the emergency department (ED). The study will be conducted in a university hospital during a 36 months period.

Inclusion and exclusion criteria

Only patients at the ED with primary diagnosis of new-onset AF, > 40 years old and that will be willing to sign the informed consent will be included in the trial. Otherwise, patients with concomitant cardiac disorders that require surgery or endovascular treatment will be excluded. As well, patients with clinical instability (systolic blood pressure ≤ 90 mmHg and/or Mean arterial pressure < 60 mmHg), acute coronary syndromes, stroke, sepsis, holiday heart syndrome, hyperthyroidism and pulmonary embolism will be excluded.

Recruitment and randomization

Emergency physicians who are not members of the intervention groups will notify the study coordinator of potential subjects that can enroll in the trial. Possible study subjects or their surrogate decision-makers will receive a clear explanation about the study trial and, if the patient agrees to participate, informed consent will be signed. Subsequently, computerized randomization between treatment provided by FAST-AF or standard of care team will be done by the National Health and Medical Research Council Clinical Trials Centre of the University of Sydney. Randomization between groups will be conducted in a 1:1 ratio using random size blocks. Moreover, strategies such as clinical trial presentation, provision of explanatory booklets on how to refer patients for the trial and study protocol supply will be made in order to enhance referral to clinical trial and recruitment rates.

Intervention and adherence

After randomization, subjects will be allocated to one of the intervention groups. The standard of care team will be formed by the ED personnel. For FAST-AF, the team will be composed of an electrophysiologist, an electrophysiologist nurse and a pharmacist. Although there are several protocols establishing AF gold standard treatment published by international cardiology societies, we selected the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation because of its worldwide use (January et al., 2014). In order to comply with the guidelines of 2014, a copy will be given to both intervention teams which will illustrate treatment care according to the up to date published guideline.

A previous study have shown that in a community hospital ED, an average of 118 patients with new-onset AF are admitted per year (January et al., 2014). Therefore, although the intervention begins at the ED, it might continue in other hospital settings such as the ward. In these cases, both teams will still conduct the patient treatment. Because the intervention will be done mainly during in-hospital stay, patient adherence to treatment is expected to be high and, therefore, not considered a source of bias. Additionally, subjects demand to change to FAST-AF group is expected to be less than 10% because arrhythmia specialist consult for the standard care team will be available anytime if needed.

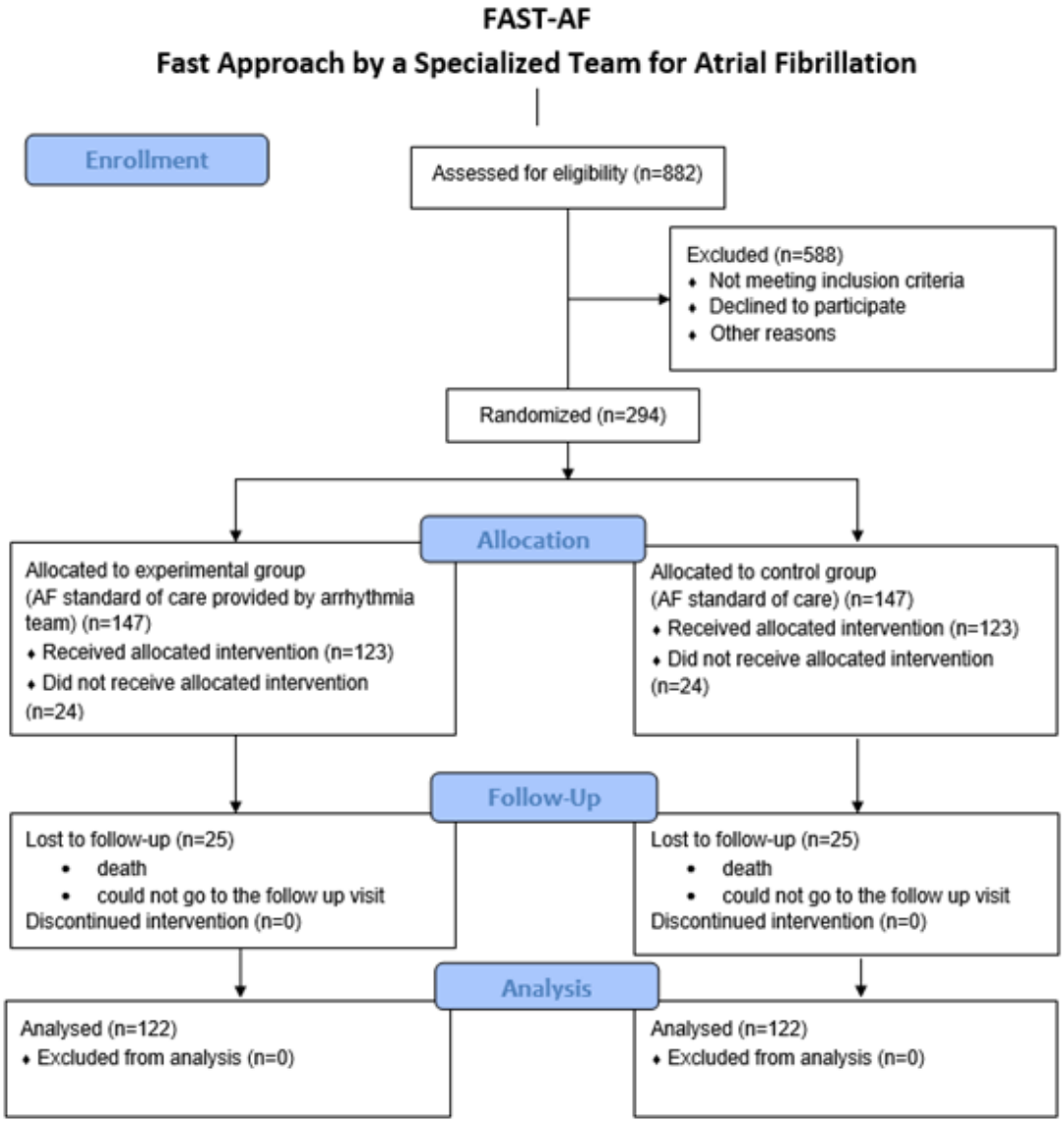
Considering the inability to effectively blind patients and staff in the emergency room, the study will be open label. However, in order to reduce detection bias, statisticians that will conduct the statistical analysis will be blinded.

Sample size conduction

Sample size calculation was made according to time to discharge rates of AF patients in the emergency room (Koenig, Ross, & Jackson, 2002; Laliberté et al., 2014; Von Besser & Mills, 2011). Assuming that 90% of the patients are discharged after 5 hours and that 10% of the patients admitted to the ward have a median time to discharge of 96 hours, an overall median time to discharge of 14.1 hours for the standard of care team was estimated. As for the arrhythmia team, a 20% reduction of the time to discharge is considered meaningful based on clinical expertise, since there is no appropriate literature data available. Consequently, it was assumed that 92% of the patients will be discharged after 4 hours and 8% of the patients admitted to the ward will have a median time to discharge of 76.8 hours. As a result, the overall median time to discharge was 9.8 hours in the arrhythmia team group. Therefore, using log-rank statistics for time-to-event comparison for the two independent groups and assuming a power of 80%, a two-sided alpha level of 0.05, a hazard ratio of 1.4388, a 10% dropout rate and a 10% crossover rate, we calculated an overall sample size of 294 subjects (147 per group). The calculation was made using Stata Statistical Software (Release 14).

Primary and secondary outcomes

In order to conduct a precise comparison between arrhythmia and control group intervention, we selected the primary and secondary outcomes according to the recommendations of the German Atrial Fibrillation



Competence NETwork and the European Heart Rhythm Association consensus conference (Kirchhof et al., 2007). Time to hospital discharge was selected as primary outcome, since it is clinically meaningful and an accurate and objective measure of AF treatment effectiveness. Secondary outcomes were selected in order to evaluate other factors that are related to the emergency department treatment and that reflect patient prognosis.

Statistical analysis

The primary outcome of the study is time to discharge from the beginning of the intervention in the emergency department until hospital discharge. The primary analysis will be made according to the intention-to-treat (ITT) principle. Kaplan-Meier curves will be plotted and assessed by log-rank statistics to test the hazard ratios between groups; 95% confidence intervals for median time to discharge will be computed for each randomized arm. Thereafter, a per protocol analysis will be conducted for the primary outcome.

Secondary outcomes and their respective statistical analysis tests are: Time to rate/rhythm control (Kaplan-Meier curves and log-rank statistics), compliance with anticoagulation at discharge (chi-squared test), readmission rates (chi-squared test), presence or absence of atrial fibrillation in a 24 hour holter monitor (chi-squared test), quality of life assessment by a the Atrial Fibrillation Effect on Quality of life survey (Student's t-test) and hospitalization costs (descriptive statistics). Statistical analysis will be performed using an established statistical software such as IBM SPSS statistics or Stata Statistical Software (Release 14).

Data management and monitoring

All patient information will be collected from the hospital patient electronic medical record and inserted in an electronic case report (Microsoft Excel spreadsheet). This will be done by a study coordinator that is certified by the Health Insurance Portability and accountability act of 1996 (HIPAA). The data will be exported to Stata Statistical Software (Release 14) to run statistical analysis based on demographic characteristics, time during ED and hospitalization, adherence to treatment and costs. Data monitoring will be done every 7 days and backed up every 14 days.

DISCUSSION

AF is the most common arrhythmia, accounting for approximately one-third of hospitalizations for cardiac rhythm disturbances. Most data regarding the epidemiology, prognosis, and quality of life in AF have been obtained in the United States and Western Europe. It has been estimated that 2.2 million people in America and 4.5 million in the European Union have AF (Fuster et al., 2006).

Previous study suggests that AF treatment should be provided by a multidisciplinary specialized team composed by an electrophysiologist, a cardiology nurse, a cardiac surgeon, a geneticist and a geriatrician (Fumagalli et al., 2016). However, considering the characteristics of patients in the emergency department setting and the study inclusion and exclusion criteria, a team composed by an electrophysiologist, a cardiology nurse, and a pharmacist is considered sufficient to conduct emergency AF treatment. As for the control group, it will be formed by an ED physician, a nurse and a pharmacist as according to current clinical practice. Moreover, since both intervention groups will be formed by different health care professionals than the ones on call in the ED, the study will not compromise the ED workflow.

Our study was designed to evaluate our primary hypothesis that AF patients treated by FAST-AF will have better outcomes regarding hospital length of stay, compliance to treatment guidelines and less AF complications. We expect a 20% reduction in time to discharge for the FAST-AF group compared to the standard care. Although the majority of patients will be discharged with a difference of a few hours between both groups, the remaining subjects that need further hospitalization will probably benefit from the intervention by FAST-AF. Additionally, in unstable patients, the specialized approach and treatment decision making will subsequently contribute to minimize AF complications, morbidity, and health care costs.

Study limitations include a selection of a narrowed population which may limit the generalization of results. Nevertheless, exclusion of patients with other comorbidities that could be a potential confounder was made in order to have an accurate evaluation of the efficacy of the FAST-AF intervention. Furthermore, exclusion criteria was based on ethical principles considering that unstable patients cannot wait for consent form approval and randomization in order to receive appropriate treatment. However, if arrhythmia team is proved to have better treatment outcomes, the study results may be reproducible in more severe cases such as the subgroup of patients that fulfill the exclusion criteria.

Additionally, single center studies may increase the chance of sampling bias. On the other hand, although a multicenter approach could be preferable to increase the enrollment rate, a single center study contribute to study costs reduction and also to a centralized recruitment,

better study monitoring, and greater study protocol adherence, which are important to increase internal validity.

Another limitation is that previous awareness of compliance to guidelines evaluation may contribute to better physician adherence to treatment protocols. Nevertheless, if FAST-AF is proven to be more effective, it is expected that specialized team will have better outcomes in out of study clinical practice situations. Future observational studies will be needed in order to validate the results.

CONCLUSION

In conclusion, our study design is readily replicable, given its simplicity and feasibility. Although implementing an open label design, to obviate potential biases during the trial, we propose blinding of statisticians. Additionally, compliance to gold standard data monitoring, and a selection of accurate objective surrogates that are not influenced by placebo effect may prevent other potential bias.

The novelty of our study consists in the evaluation of the effectiveness of a multidisciplinary specialized team in the emergency AF management. If proven to have better outcomes, future studies can be conducted in order to address if the results can be similarly achieved by using specialized multidisciplinary teams consultation by virtual meeting platforms (Dudzinski & Piazza, 2016; Kabrhel et al., 2016).

All things considered, AF is a prevalent disease that may cause several complications and morbidity. It is related to social and financial burden. The diversity of treatment options available and the lack of adherence to the updated guidelines may compromise AF therapy success. In outpatient clinics, multidisciplinary specialized arrhythmia team treatment was associated with better outcomes in patients with AF. We propose a study to evaluate if the specialized treatment has an impact on the AF emergency care. If proven to have better outcomes, FAST-AF may lead to a better prognosis, improvement of quality of life and reduction of the overall health care costs.

Acknowledgment

The authors are sincerely thankful to the PPCR faculty for helping with the knowledge, which provided insight and expertise that greatly assisted to finalize the manuscript. Also, the authors would like to express their sincere gratitude to Dr. Felipe Fregni, Dr. Tanya Morosoli, Dr. Miluska Bromley, Dr. Ines Mesia, Dr. Felipe Piccarone, Dr. Ugur Damar, Dr. Arturo Tamayo, Dr. Ben Illigens, Janice Breeze, MPH, Dr. Clarissa Valim, and Dr. Sandra Marques Silva for exemplary guidance, valuable feedback and constant encouragement throughout the duration of the project.

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Conflict of interest and financial disclosure

The authors have no personal or financial conflicts of interest to declare. No funding was received for this research proposal.

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