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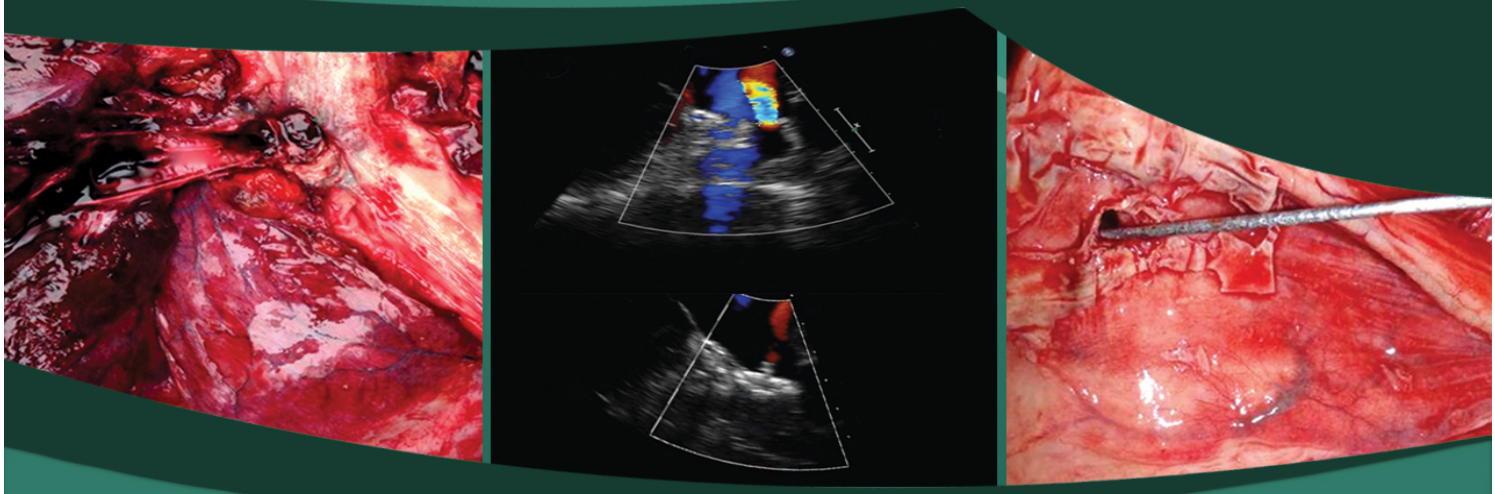

- Contact-Force Guided Posterior Wall Isolation as an Adjunctive Ablation Strategy for Persistent Atrial Fibrillation
- Fluoroless Catheter Ablation of Atrial Fibrillation: Integration of Intracardiac Echocardiography and Cartosound Module
- Contact-Force Guided Posterior Wall Isolation as an Adjunctive Ablation Strategy for Persistent Atrial Fibrillation
- Extensive Left Atrial Low-Voltage Area During Initial Ablation is Associated with A Poor Clinical Outcome Even Following Multiple Procedures

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Contents

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Editorial

Journal of Atrial Fibrillation

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OMICRON is here.... and life must go on!!

Journal of Atrial Fibrillation (JAFIB)

Aug - Sep 2021

Issue 2

Volume 14

Dear Colleagues

Welcome to the November issue of JAFIB. Hope you had a great Thanksgiving weekend. It was a great closure to fall and winter festivities seem to have already begun. Congratulations to the APHRS team on a very successful Annual Meeting in Shanghai, China! It was a well rounded meeting with excellent science being discussed. The hybrid model of delivering high quality content through both in person and Telemedia seem to have worked well. American Heart Association also completed their annual sessions with lot groundbreaking data on various topics in cardiovascular medicine.

While the governments across the world work towards effective vaccination drives, OMICRON showed up in South Africa. It has already made its way to most of the countries across the world. Our vows in dealing with the global pandemic have not come to a stop yet. As Dr. Anthony Fauci said "COVID is not going anywhere, it is here to stay, and we have to learn how to live with it". In this issue of JAFIB, we have several important manuscripts covering a broader area of AF pathophysiology and management.

We have some very important changes coming to the journal. Starting January 1, we will have a new editorial board and a new Editor-in-Chief. Dr. Andrea Natale, the founding Editor-in-Chief for JAFIB is going to take up the responsibilities again. With improved content and new look, we will continue to deliver you high quality research and data totally free in open access format.

Sincerely
Amin-Al-Ahmad

Amin-Al-Ahmad
MD, FACC, FHRS

Interim Editor-in-Chief
Journal of Atrial Fibrillation

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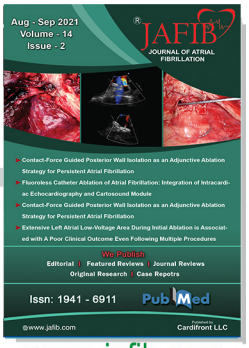

The Importance Of Atrial Fibrillation's Associated Comorbidities as Clinical Presentation and Outcome Contributors

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Abstract

Atrial fibrillation (AF) has a heterogeneous clinical presentation. It can occur: (a) in the presence or absence of detectable heart disease, and, (b) with or without related symptoms. Its prognosis in terms of thromboembolism and mortality is most benign when applied to young individuals (aged less than 60 years) without clinical orecho cardio graphic evidence of cardiopulmonary disease [termed "lone AF"]. However, by virtue of aging or because of the development of concomitant cardiovascular disorders, patients move out of the lone AF category over time, accompanied by increased risks for thromboembolism and mortality. Thus, underlying and/or associated comorbidities must play an important role in the presentation and consequences of patients with AF. While, no doubt, most clinicians likely appreciate that the majority of the AF patients they see have associated cardiovascular, pulmonary, metabolic, endocrinologic, genetic, and/or other disorders, it is not clear how much they appreciate that these disorders directly relate to the presenting symptoms and to the risks from AF in addition to their role as risk factors (or markers) for AF. This issue is the subject of this review manuscript.

Introduction

Atrial fibrillation (AF) has a heterogeneous clinical presentation. It can occur: (a) in the presence or absence of detectable heart disease, and, (b) with or without related symptoms. Its prognosis in terms of thromboembolism and mortality is most benign when applied to young individuals (aged less than 60 years) without clinical orecho cardio graphic evidence of cardiopulmonary disease [termed "lone AF"]. However, by virtue of aging or because of the development of concomitant cardiovascular disorders, patients move out of the lone AF category over time, accompanied by increased risks for thromboembolism and mortality. Thus, underlying and/or associated comorbidities must play an important role in the presentation and consequences of patients with AF. While, no doubt, most clinicians likely appreciate that the majority of the AF patients they see have associated cardiovascular, pulmonary, metabolic, endocrinologic, genetic, and/or other disorders, it is not clear how much they appreciate that these disorders directly relate to the presenting symptoms and to the risks from AF in addition to their role as risk factors (or markers) for AF. This issue is the subject of this review manuscript.

According to the 2001 ACC/AHA/ESC Guidelines for the Management of Patients With Atrial Fibrillation (AF): (1) "AF has a heterogeneous clinical presentation, occurring in the presence or absence of detectable heart disease or related symptoms…The prognosis associated with AF in terms of thromboembolism and mortality is most benign when applied to young individuals (aged less than 60 years) without clinical orecho cardio graphic evidence of cardiopulmonary disease [descriptors for what has been termed "lone AF"]. These patients have a favorable prognosis with respect to thromboembolism and mortality. By virtue of aging or the development of cardiac abnormalities, however, patients move out of the lone AF category over time, and the risks of thromboembolism and mortality rise."[1]

The subsequent versions of these guidelines from 2006 through 2019 do not expound further on these comments. Implied in this statement is the importance that the underlying and/or associated comorbidities play in the presentation and consequences of patients with AF. While, no doubt, most clinicians likely appreciate that the majority of the AF patients they see have associated cardiovascular, pulmonary, metabolic, endocrinologic, genetic, and/or other disorders, it is not clear how much they appreciate and remember when facing a patient that these disorders directly relate to the presenting symptoms and to the risks from AF in addition to their role as risk factors (or markers) for AF.

Key Words

Atrial Fibrillation; Lone Atrial Fibrillation; Comorbidities; Thromboembolism

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"Lone AF" Can Be Instructive

"Lone AF" (or, as it was originally called, lone auricular fibrillation) is a term that was coined almost a century ago to indicate AF in the absence of associated causative structural disorders. It has also been described as benign AF, idiopathic AF, functional AF, fibrillation of

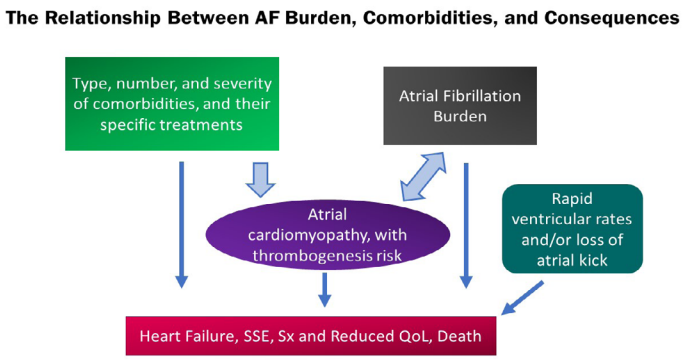

Figure 1: **The relationship between atrial fibrillation burden, comorbidities, and consequences.**

AF = atrial fibrillation. SSE = stroke and systemic embolism. Sx = symptoms. QoL = quality of life. Heart failure, thromboembolic risk, symptoms, reduced quality of life, and/or death may be directly consequent to the number, type, and severity of comorbidities present in a patient with or without AF, to the rapid ventricular rate in the presence of AF, and/or to the amount of AF present (AF burden). Both the comorbidities and the AF burden are co-contributors to the atrial cardiomyopathy present in AF patients, to the extent of the atrial cardiomyopathy, and to its thrombogenic potential.

unknown origin, and fibrillation without heart disease.[2] In that era, the diagnostic tools available to detect possible underlying cardiovascular (CV) disorders consisted of the medical history, detailed physical examination, electrocardiography, phonocardiography, Master's 2-step exercise test, and chest x ray. Quite likely, some patients classified then as "lone AF" would now be reclassified using modern diagnostic methods. In fact, multiple studies during the past few decades have revealed histopathological changes in atrial tissue obtained from apparently "lone AF" – most commonly inflammation and/or fibrosis [3-9]–which indicate that subclinical atrial alterations are often present in patients otherwise labelled" lone AF." Additionally, gene-related causes for some of the patients have also become apparent as has later in life hypertension in up to 40% or more.[10,11] Moreover, despite the absence of structural heart disorders, some "lone AF" patients have recognized precipitants for their events, such as parasympathetic, sympathetic, alcohol, stimulant, or sleep-apneic triggers. Nonetheless, important clinical observations were made in apparently "lone AF" patients in decades past that can teach us important messages now. These, coupled with observations in patients with AF plus associated disorders can inform us of the multiple ways such disorders interact with/affect the presentations and outcomes of the very many my riad of patients we encounter with AF.

Symptoms

AF can be symptomatic or asymptomatic, even in the same patient. Symptoms can vary with the ventricular rate, underlying functional status, frequency/duration/burden of AF, and individual patient perceptions.[1,12,13] Additionally, most patients with AF complain of palpitations, chest pain, dyspnea,fatigue, or lightheadedness.[1,12,13] Less frequent are thromboembolic events, overt syncope, acute ischemic events, or acute heart failure. Importantly, none of these symptoms are specific for AF, as each may result from many disease states. Nonetheless, the question should be asked as to whether and which of these symptoms result primarily from atrial fibrillation versus from or synergistically consequent to underlying cardiovascular comorbidities [figure 1]. The answer is important because for those that are substantially linked to the underlying comorbidities, elimination of AF, whether by drugs and/or ablation may not provide any certainty of relief -- a major point of focus behind this manuscript. It is through an examination of "lone AF" that answers may become apparent and hence the contributions of comorbidities best appreciated.

Clinical Presentation of Lone AF

In almost all patients with AF, the immediately proximate instigators of AF are abnormalities that are present in the left atrium. These are anatomic, histopathologic, contractile, electrophysiologic, and endothelial.[1,12,13] These atrial cardiomyopathic alterations are the result of mechanisms linked to underlying comorbidities and/or alterations due to AF itself via an atrial tachycardic myopathic effect [14-17][figure 2]. In themselves, these atrial alterations do not directly produce systemic symptoms, although their etiologies can. For example, hypertension may result in LV hypertrophy with reduced diastolic compliance and increased LV pressures. These, in turn, may result in left atrial anatomic and functional alterations, increases in LA pressure, and consequent dyspnea. Accordingly, it is the elevated LV pressures that are the major factor leading to dyspnea, rather than dyspnea being just a result of LA alterations. Superimposed, dyspnea may worsen with impaired LA emptying and loss of AV synchrony if AF also develops in this physiologic setting. [figure 1] In contrast, palpitations are likely the symptom that is most directly linked to AF itself. The sense of palpitations is a consequence of the change in pulse rate and rhythm that occurs with the development of AF. Palpitations are not noted by all AF patients, but when they are, they are a direct result of the arrhythmia. Other symptoms commonly seen in patients with AF, and perhaps most prominent during AF, such as dyspnea, chest discomfort, hypotensive- or reduced cardiac output-associated, require impairment of LV compliance, alterations in systolic output, ischemia, etc., as contributing mechanisms. If the above is all true, then "lone AF"should have palpitations as the major or only symptom – particularly if paroxysmal rather than chronic. This, in fact, is the case.

In their 1954 manuscript titled Lone Auricular Fibrillation, Evans and Swann (2) reported on 20 patients with "lone AF" and found that: "Many of the patients were free from symptoms and the arrhythmia was found at a medical examination conducted for reasons unconnected with the heart…The single relevant complaint was palpitations, which were present in 11 of the patients.""Shortness of breath was sometimes present, …but was always explained by aging, obesity, or commencing emphysema." "Symptoms were absent in the other 9 patients." This report was consistent with an earlier but smaller series published by Master and Eichert[18] in which 5 naval officers, ages 23-48, were diagnosed with "functional paroxysmal auricular fibrillation." All were without any evident associated cardiovascular disease. "Palpitation of the heart is the chief presenting symptom" was noted in each case; in two, there was a GI trigger and a sense of "distension." In some, there was associated lightheadedness if standing and exerting. No other cardiovascular symptoms were reported. Six additional reports from 1930 to 1968 also report palpitations as the most common symptom in patients with "lone AF." [19-24] Some had associated fatigue, "anxiety", "weakness", dizziness, sweating; some were asymptomatic. Mild dyspnea or chest discomfort was infrequently reported in these six papers.Not yet adequately investigated is any possible relationship between age and the awareness of palpitations in "lone AF." If, with age, for example, a patient was to develop AV nodal conduction dysfunction in association with the electrical disorder causing AF (such as may

occur in the brady-tachy syndrome patient), the ventricular rate during paroxysmal AF may slow, which might possibly alter the sense of palpitations.

While it is possible that in some of the above-reported patients, modern diagnostic methodologies might reveal mild structural heart disease or biopsies might reveal altered atrial histology, such findings would not change the observation that the overwhelmingly dominant presenting symptom, when one was present, was palpitations. Consequently, these finding suggest that when AF presents with substantial cardiovascular or pulmonary symptoms, underlying comorbidities are likely playing a role that should be addressed beyond rhythm control of the AF.

Consistent with these observations is the recent report regarding the presence of symptoms as predictors of monitor-detected subclinical AF (SCAF). In the recent REVEALAF trial, in which an inserted cardiac monitor (ICM) was used in a demographically enriched population to assess the frequency and characteristics of SCAF, [25] a substudy assessment of symptoms as predictors of detecting SCAF determined that only palpitations had an association with AF detection when controlling for other baseline symptoms (hazard ratio 1.61 (95%CI 1.12-2.32; p=0.011). [26] No other symptom studied, including dyspnea, chest pain, syncope, dizziness, or fatigue, was associated with an increased likelihood of SCAF detection. Yet, patients without detected SCAF had an even higher frequency of such other cardiovascular symptoms than those with detected SCAF.

Clinical Consequences

The most feared clinical consequences of AF are thromboembolism and death. Heart failure (HF), impaired quality of life (QoL), need for hospitalization, costs are additional issues of concern. Here, again, "lone AF" can be contrasted with AF plus associated disorders, but with greater difficulty. The ACC/AHA/ESC practice guidelines [1,12] note that "the rate of stroke in patients with AF is related to coexistent cardiovascular disease. In a small, retrospective, population-based study in Olmsted County, Minnesota, over 3 decades, the 15-year cumulative stroke rate in people with lone AF (defined as those younger than age 60 years with no clinical history or echocardiographic signs of cardiopulmonary disease) was 1.3% per year."[1,12] In a larger, 30-yr follow up series reported by this same investigative center, "overall survival of the 76 patients with lone atrial fibrillation was 92% and 68% at 15 and 30 years, respectively, similar to 86% and 57% survival for the age- and sex-matched Minnesota population. Observed survival free of heart failure was slightly [but not significantly] worse than expected (p=0.051). Risk for stroke or transient ischemic attack was similar to the expected population risk during the initial 25 years of follow-up but increased thereafter (p=0.004), although confidence intervals were wide. All patients who had a cerebrovascular event had developed at least 1 risk factor for thromboembolism." [27] They concluded that "Comorbidities significantly modulate progression and complications of atrial fibrillation. Age or development of hypertension increases thromboembolic risk."

In accordance with the above, the ACC/AHA/HRS and ESC guidelines do not recommended anticoagulation for stroke prevention in patients with lone AF. However, they note that thromboembolic risk increases progressively as concomitant risk disorders increase [using the $CHADS_2$ score where C = congestive heart failure, H = hypertension, A = age 75 yrs or above, D = diabetes, and S = prior stroke/systemic embolism or transient ischemic attack] and that elevated risk scores call for chronic oral anticoagulation. This strategy has not changed in concept during ensuing years. As noted by the 2020 ESC guidelines (11) common stroke risk factors are now summarized in the clinical risk-factor-based CHA_2DS_2-VASc score [C = congestive heart failure, H = hypertension, A = age 75 years or older, D = diabetes mellitus, S = stroke/systemic embolism/prior TIA, V = vascular disease, A = age 64-74, Sc = Sex category (female)]. These 2020 guidelines recommend no anticoagulation for a score of 0 in men or 1 in women. [Similarly, but not identically, the 2019 ACC/AHA/HRS guidelines recommend no anticoagulation for men with a score 0-1or women with a score 0-2.] However, higher scores come with recommendations for chronic oral anticoagulation, again driven by the presence of specific comorbidities. The particular difficulty with "lone AF" is the fact that aging does not protect these patients from developing the comorbidities that commonly appear in older populations, including hypertension, diabetes, vascular disease, obesity, and the like. Accordingly: (1) it is difficult to determine a true risk for thromboembolic events, or mortality, or heart failure associated with "lone AF", as we would no longer call it "lone AF" if we encountered the same patient later in life, after hypertension and coronary artery disease, for example, were to have developed; (2) even in the "lone AF" population, as with the non-lone AF population, there is data to suggest that thromboembolic risk is greater for non-paroxysmal AF versus paroxysmal AF, and in association, the risk is greater in those that have or who develop atrial enlargement or atrial dysfunction as determined by imaging;[10,11,28,29] and,[3] different series of "lone AF" patients that consist of different ages, different AF patterns, and different durations of follow up will accordingly find different rates of outcome events. For example, Scardi et al.[30] reported yearly stroke rates in "lone AF" of 1.1% for paroxysmal AF but 16.3% for chronic AF (mean follow up period 10 years); Brand et al.[31] reported stroke rates of 28% in "lone AF, in the Framingham

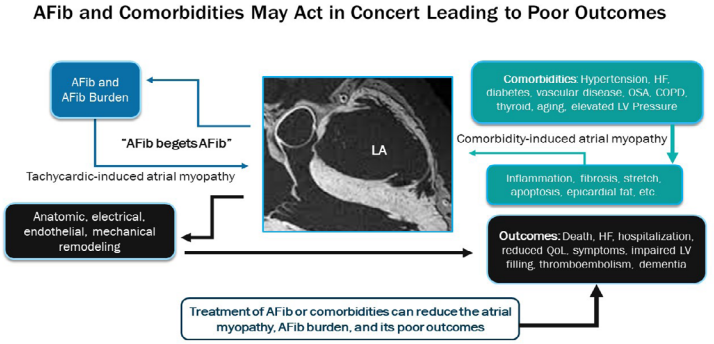

Figure 2: Atrial fibrillation and comorbidities may act in concert (synergistically) leading to poor outcomes in patients with atrial fibrillation

AFib = atrial fibrillation. HF = heart failure. OSA = obstructive sleep apnea. COPD = chronic obstructive pulmonary disease. LV = left ventricle/left ventricular. QoL = quality of life. Comorbidities present in patients with AF can produce histopathologic, anatomic, mechanical changes in the left atrium that result in an atrial cardiomyopathy. These changes, with associated electrophysiological alterations can result in the development of atrial fibrillation. Atrial fibrillation itself can contribute to and further worsen atrial cardiomyopathic changes, resulting in more atrial fibrillation (Afib begets Afib) which is a detrimental loop in the progression of this process. The altered atrial function (including endothelial dysfunction) can be prothrombotic, resulting in stroke and systemic embolism, as well as resulting in impaired ventricular filling and systolic function, higher pulmonary vascular pressures, and adverse outcomes associated there with.

data base but 7 of the 8 patients had chronic rather than paroxysmal AF (mean follow up period 30 years); Rienstra et al.[32] reported stroke rates of 3% in the "lone AF" patients who participated in the RACE study (mean follow up period 2.3 years); and Kopecky et al.[33] reported stroke rates in Olmsted County, MN of 4% in "lone AF" (mean follow up 14.8 years). Regardless of such differences, we should feel certain that comorbidities play an important role in the clinical presentation and prognosis associated with AF, whether they have a causative role in the development of AF and/or a modifying role in the consequences associated with AF.

Recently, the roles of AF and concomitant comorbidities re: thromboembolic risk have been further clarified with studies that have compared event rates in patients with lone AF, AF plus comorbidities, and comorbidities without AF. In 2009, Botto and colleagues [34] introduced this concept when they reported that stroke risk was dependent upon both AF presence and duration plus $CHADS_2$ score. Using data from 568 patients with known AF and implanted pacemakers, they identified two subpopulations with markedly different risks of thromboembolic events: 0.8% vs 5% (p=0.035). The former corresponded to no device-detected AF and a $CHADS_2$ score = 2 or less, or AF 5 minutes with $CHADS_2$ score= 1 or less, or AF 24 hours with $CHADS_2$ score = 0. In contrast, thromboembolic rates rose progressively as AF duration increased and/or as CHADS2 score increased in patients with a $CHADS_2$ score of >2 to >5. In 2019, similar findings were reported in a larger series by Kaplan et al. (35)They determined rates of stroke and systemic embolism in 21,768 non-anticoagulated patients with implantable electronic devices capable of continuous AF monitoring using electronic health records. Maximal AF duration and CHA_2DS_2-VASc scores were assessed, with AF burdens categorized as no AF, AF 6 min-23.5 hours, AF >23.5 hours. "Both increasing AF duration (p<0.001) and increasing CHA_2DS_2-VASc score(p<0.001) were significantly associated with annualized risk of stroke and systemic embolism." Stroke and systemic embolism rates were low in patients with a CHA_2DS_2-VASc score of 0 to 1, regardless of detected AF duration but rose to >1%/year in patients with a CHA_2DS_2-VASc score of 2 with >23.5 hours of AF and in those with a CHA_2DS_2-VASc score of 3-4 plus > 6 minutes of AF, and in patients with a CHA_2DS_2-VASc score of 5 or higher, even with no AF. Concordantly, Singleton et al [36] reported on observations from the REGARDS study (Reasons for Geographic and Racial Differences in Stroke) in which 28,253 patients were classified into 1 of 4 groups based upon the presence or absence of AF and the presence or absence of cardiovascular comorbidities. During 244,560 person-years of follow-up (median 8.7), 1206 strokes occurred. Compared with patients with neither AF nor cardiovascular comorbidities, there was no increased stroke risk among patients with AF alone (hazard ratio 1.23; 95% CI 0.62-2.18 [p=0.511]). However, patients without AF but with cardiovascular comorbidities had an increased risk of stroke (hazard ratio 1.77; 95% CI 1.48-2.18 [p<0.0001]) and specifically cardioembolic stroke (hazard ratio 2.34; 95% CI 1.48-3.90 [p=0.002]). These data sets are consistent with the impression that "lone AF" has a low risk of thromboembolism [likely because atrial pathophysiology is minimal – unless, perhaps, the AF is chronic] and that cardiovascular comorbidities contribute significantly to the thrombosis-prone atrial myopathy and hence embolic risk.

Conclusion

Patients with AF are prone to symptoms and to adverse outcomes. However, the type and severity of symptoms differ in patients with "lone AF" from those with AF plus cardiovascular comorbidities. Palpitations are the most prominent symptom in "lone AF" whereas the likelihood or severity of dyspnea, chest discomfort, hemodynamic impairment, and the like are increased in the presence of associated cardiovascular and related comorbidities. Similar symptoms, however, can occur in patients with cardiovascular disorders without accompanying AF, though they may be more pronounced when AF is also present, due to the effects of reduced ventricular filling time, loss of atrial contraction, and loss of AV synchrony consequent to the AF. Similarly, patients with "lone AF" appear to have a lower risk for major morbidity and death than patients with AF plus cardiovascular comorbidities. However, since such comorbidities may develop later in life, categorizing a patient as having "lone AF" does not mean that its more benign course will remain as such as the patient ages. Thus, continued vigilance and reevaluation of the AF patient is required during the course of clinical follow up – especially if a change in symptoms is noted. Finally, it now appears likely that simply classifying a patient as having or not having AF, whether lone or not, is no longer sufficient. We must also appreciate the presence/absence and importance of any associated left atrial cardiomyopathy – especially its key role in stroke risk. In such a construct, the role of AF as a risk factor for thromboembolism must encompass enough AF to contribute to the myopathic alterations that reach the threshold necessary for thrombogenesis. With lone AF, absent associated cardiomyopathies, such a threshold is rarely reached. Additionally, the length of AF runs and total AF burden must be more important than occasional relatively short episodes of paroxysmal AF. Simultaneously, the greater the number and severity of associated contributory comorbidities, the shorter might be the AF runs that become importantly contributory. Thus, notably, in this framework, the presence or absence of any AF-associated symptoms is not important with respect to atrial myopathic thrombogeneisis and stroke risk. Accordingly, it is not surprising that the very recent manuscript by the GARFIELD-AF registry investigators (which did not include patients with lone AF) noted that major outcomes (stroke, bleeding) do not differ between symptomatic and asymptomatic AF presentations. [37] However, adverse outcomes as well as symptomatic presentations are different in patients with versus without associated comorbidities, as well as which ones and their severity.

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Incidence of New Onset Atrial Fibrillation After Cardiovascular Surgery in Vietnam: Results From A Novel Screening Strategy

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Abstract

Objectives: To examine the incidence of atrial fibrillation (AF) newly developed after cardiovascular surgery in Vietnam, its associated risk factors, and postoperative complications. We also sought to evaluate the feasibility of a novel screening strategy for post-operative AF (POAF) using the combination of two portable devices.

Methods: Single-centre, prospective cohort study at the Cardiovascular Centre, E Hospital, Hanoi, Vietnam. All patients aged≥18 years, undergoing cardiovascular surgery and in sinus rhythm preoperatively were eligible. The primary outcome was occurrence of new-onset POAF detected by hand-held single-lead electrocardiography (ECG) or a sphygmomanometer with AF-detection algorithm. Multivariate logistic regression was used to identify risk factors of developing post-operative AF. Feasibility was evaluated by compliance to the protocol and semi-structured interviews.

Results: 112 patients were enrolled between 2018-2019: mean age 52.9±12.2 years; 50.9% female; 92.0% (n=103) valve surgery; 9.8% (n=11) coronary surgery. New-onset POAF developed in 49 patients (43.8%) with median time to onset 1.27days (IQR 0.96 -2.00 days). Age≥65 years was the only significant risk factor for the development of POAF(OR 3.78, 95% CI 1.16-12.34).The median thromboembolism risk scores (CHA_2DS_2-VASc score) were comparable among patients with and without POAF (1.0 vs. 1.0, p=0.104). The occurrence of POAF was associated with higher rates of postoperative complications (24.5% vs. 3.2%, p<0.001). Both doctors and nurses found this screening strategy feasible to be implemented long-term with the main difficulties being the instructions on both devices were in English, and an increase in workload.

Conclusions: In this single-centre study, new-onset POAF occurred in 43.8% of patients who underwent cardiovascular surgery. This novel POAF screening strategy was feasible in a low resource setting, and its implementation could be improved by providing continuous training and translation to local language.

Introduction

Up to 80% of patients undergoing cardiac surgery could develop new atrial fibrillation (AF) – a cardiac rhythm disorder[1]. Besides its high incidence, this arrhythmia is also associated with a higher risk of stroke, and worse surgical outcomes including higher risk of death, infections, prolonged length of stay, and increased healthcare cost [2].

In Vietnam, data regarding AF are sparse, with only three studies identified in the literature. One study has shown the estimated the prevalence of AF among elderly patients admitted to the National Geriatric Hospital was 3.9%, among which 22.9% did not receive guideline-recommended anticoagulation[3]. The other two studies, in surgical settings, focused on treatment of pre-existing AF with one investigating the use of intraoperative amiodarone (an anti-arrhythmic drug)[4] and the other examining the application of an additional Cox-Maze procedure[5]. To our knowledge, evaluation of new-onset post-operative AF (POAF) has never been conducted in Vietnam, in part due to the limited resources for screening. Therefore, it is important to examine the incidence of POAF in Vietnam to provide more insights into this common post-surgical complication.

Accordingly, we developed a novel POAF-screening strategy using two devices that could detect AF with high specificity and sensitivity while minimally increase the workload of the involved staff. We sought

Key Words

Atrial Fibrillation, Screening, Cardiovascular Surgery.

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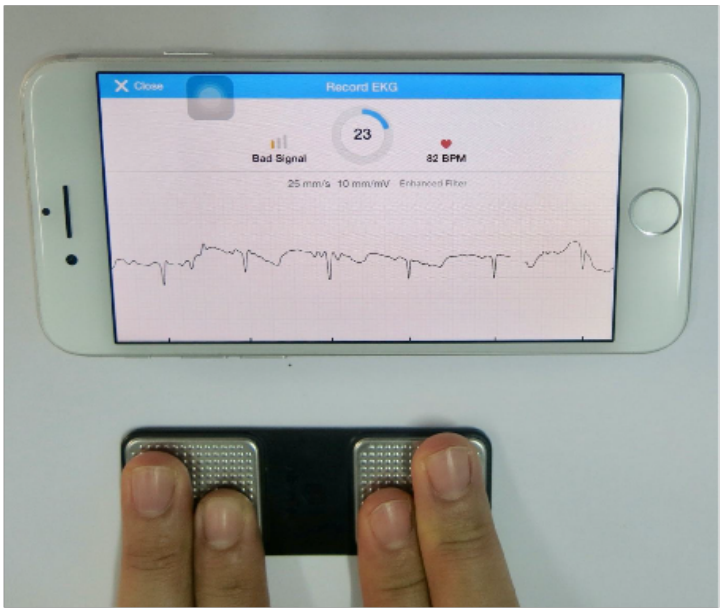

Figure 1: **AliveCorKardia Mobile device and app.**

Reused from Ngo et al[6].

to investigate the incidence of POAF, its associated risk factors and its association with other postoperative complications. The results of this study will provide preliminary data regarding POAF, increase the awareness of this common disorder, and assist efforts to improve POAF detection and outcomes after cardiovascular surgery in Vietnam.

Methods

Study design

This was a prospective single-centre study testing a novel strategy to screen for POAF, at the Cardiovascular Centre, E Hospital, Hanoi Vietnam between August 2018 – December 2019. Ethical approval was granted by the Scientific Board of Cardiovascular Centre, Hanoi, Vietnam (reference number 2862). The full study protocol has been published previously [6], and is summarised in brief below.

Participants

Consecutive patients who were ≥18 years old, undergoing coronary artery bypass graft (CABG) surgery and/or valve surgery and in sinus rhythm prior to operation were eligible for inclusion. Patients with known AF (we did not screen for history of atrial flutter), congenital heart diseases, and those with 3rd degree atrioventricular nodal block requiring pacemaker after surgery were excluded. Written informed consent was obtained from all participants.

POAF Screening strategy

In brief, participants were screened for POAF daily from day-1 post-surgery until hospital discharge. During their Intensive Care Unit (ICU) stay, nursing staff reviewed the participants bedside patient monitor hourly for heart rate observations (as part of usual care). If AF was suspected on the monitor, then a 30-second single-lead ECG recording was taken to document the participant's heart rhythm using the hand-held smartphone Alive CorKardia Mobile device (Figure 1) as no facility exists to print the trace from the bedside monitor. The Alive CorKardia device records a 30-second single-lead ECG, and provides an automated algorithm diagnosis with a sensitivity of 98% and specificity of 97% [7].

When a patient was transferred from ICU to the Department of Thoracic and Cardiovascular Surgery, POAF screening was then performed 3-times a day using the Micro life BP200 Afib sphygmomanometer (Figure 2) instead of the standard-care BP monitor. The Micro life sphygmomanometer records three consecutive measurements and uses an algorithm to automatically detect irregular heart rhythm [8]. If AF was suspected, a single-lead ECG was recorded using the Alive CorKardia Device.

If AF was suspected, the treating physicians were notified to review the patient and the single-lead ECG trace, ordering a 12-lead ECG where necessary. All ECGs were reviewed and confirmed by the investigator (Dr Do), and AF episodes ≥30 seconds were classified as POAF (refer to Supplemental Figure S1 for a detailed pathway of POAF screening).

Outcomes

• The incidence of POAF: the percentage of patients with new-onset AF after cardiac surgery out of the total number of patients included in the study (measured with the Alive CorKardia Mobile and confirmed with a 12-lead ECG).

• Feasibility of monitoring cardiac surgery patients for POAF during their inpatient stay, in Cardiovascular Centre, E Hospital (evaluated by compliance to the protocol, and qualitative process evaluation data using semi-structured interviews with doctors and nurses involved in the screening for POAF). The structured interview is included as supplementary appendix.

• Thromboembolic and bleeding risk profile of patients with POAF (measured using the CHA_2DS_2-VASc score and HASBLED score)[9].

• Risk factors associated with development of POAF: including demographic data, types of heart disease, co-morbidities, clinical laboratory tests, and intraoperative parameters.

• Postoperative complications associated with POAF: including infections, ICU length of stay, postoperative hospital length of stay, reoperation, and bleeding events.

Statistical analysis

Data are presented as frequencies and percentages for categorical variables. For continuous ones, data are presented as mean and standard deviation (SD) if normally distributed (if the mean and median are quite similar) or median and interquartile range (IQR) otherwise. Differences between groups were compared using student T-test or Mann-Whitney U-test for continuous variables and Chi-square or Fisher's exact test for categorical variables where appropriate. We also reported the difference in means or medians among patients with POAF and those without POAF. The corresponding 95% confidence intervals (CI) were estimated using the mean and standard deviation of each group [10] or bootstrapping techniques with 1000 replications

Table 1: Baseline characteristics of the study cohort.

Characteristics	Overall cohort N=112	With POAF N= 49	No POAF N=63	Difference in means or medians (mean and 95% CI)	P value*
Age (mean ± SD)	52.9 ± 12.2	55.2 ± 13.5	51.1 ± 10.9	4.2 (-0.5 – 8.8)	0.074
Age group					
<65 years old	92 (82.1%)	35 (71.4%)	57 (90.5%)		0.009
≥65 years old	20 (17.9%)	14(28.6%)	6 (9.5%)		
Female	57 (50.9%)	27 (55.1%)	33 (52.4%)		0.432
BMI (kg/m², mean ± SD)	21.7 ± 3.2	21.6 ± 3.7	21.7 ± 2.9	-0.1 (-1.4 – 1.1)	0.867
Total LOS (median [IQR]) (days)	22.0 (18.0 – 29.0)	27.0 (21.0 – 35.0)	21.0 (17.0 – 24.0)	6 (1.3 – 10.7)	0.002
Post-operative LOS (median [IQR]) (days)	12.0 (10.0 – 17.0)	15.0 (11.0 – 23.0)	11.0 (9.0 – 14.0)	4 (1.5 – 6.5)	0.003
ICU LOS (median [IQR]) (days)	4.0 (3.0 – 6.5)	6.0 (4.0 – 8.0)	3.0 (3.0 – 5.0)	3 (1.3 – 4.7)	<0.001
Type of surgery					
Coronary artery surgery	11 (9.8%)	4 (8.2%)	7 (11.1%)		0.753
Valve surgery	103 (92.0%)	47 (95.9 %)	56 (88.9%)		0.175
Combined surgery	2 (2.0%)	2 (4.1%)	0 (0.0%)		0.189
Type of valvular disease					
Aortic valve surgery	52 (46.4%)	22 (44.9%)	30 (47.6%)		0.775
Mitral valve surgery	61 (54.5%)	29 (59.2%)	32 (50.8%)		0.376
Surgery involved more than one valve	29 (25.9%)	15 (30.6%)	14 (22.2%)		0.315
Type of prosthetic valve used					
None	18 (16.1%)	10 (21.3%)	8 (14.3%)		0.159
Bioprosthetic	34 (33.0%)	19 (40.4%)	15 (26.8%)		
Mechanical	30 (29.1%)	9 (19.2%)	21 (37.5%)		
Autologous pericardium	21 (20.4%)	9 (19.2%)	12 (21.4%)		
Cardiac comorbidities					
Hypertension	25 (22.3%)	12 (24.5%)	13 (20.6%)		0.627
Vascular disease	16 (14.3%)	10 (20.4%)	6 (9.5%)		0.102
Coronary artery disease	12 (10.7%)	5 (10.2%)	7 (11.1%)		0.878
Heart failure	16 (14.3%)	9 (18.4%)	7 (11.1%)		0.276
Non-cardiac comorbidities					
Diabetes	9 (8.0%)	6 (12.2%)	3 (4.8%)		0.176
History of stroke	3 (2.7%)	2 (4.2%)	1 (1.6%)		0.577
Renal failure	43 (38.4%)	22 (44.9%)	21 (33.3%)		0.212
Chronic hepatitis	3 (2.7%)	3 (6.1%)	0 (0.0%)		0.081
Chronic lung disease	4 (3.6%)	2 (4.1%)	2 (3.2%)		1.000
Thyroid disease	3 (2.7%)	1 (2.0%)	2 (3.2%)		1.000
CHA_2DS_2-VAScscore (median, IQR)	1 (0 – 2)	1 (1 – 2.5)	1 (0 – 2)	0 (-0.6 – 0.6)	0.155
HASBLED score (median, IQR)	0 (0 – 1)	0 (0 – 1)	0 (0 – 1)	0 (-0.7 – 0.7)	0.201
Pre-operative echocardiography					
Left ventricular ejection fraction (%, mean±SD)	63.2 ± 11.8	63.4 ± 11.8	63.1 ± 11.9	0.4 (-4.0 – 4.8)	0.870
Left ventricular diameter (mm, mean±SD)	53.0 ± 11.7	54.0 ± 12.2	52.3 ± 11.5	1.7 (-2.8 – 6.1)	0.455
Left atrial parameter (mm, mean±SD)	42.3 ± 8.8	43.3 ± 8.6	41.6 ± 8.9	1.7 (-1.5 – 5.0)	0.301

Footnote: CI=confidence interval, SD=standard deviation, BMI=body mass index, LOS=length of stay, IQR=interquartile range, ICU=intensive care unit, eGFR=estimated glomerular filtration rate, CHA2DS2-VASc score=a score to evaluate stroke risk of patients with atrial fibrillation (C=Congestive Heart Failure, H=hypertension, A=Age, D=Diabetes, S=Stroke, Vasc=Vascular disease), HASBLED score= a score to evaluate major bleeding risk of patients with atrial fibrillation (H=Hypertension, A=Abnormal liver or kidney function, S=Stroke, B=history of major Bleeding, L=Labile international normalised ratio, E=Elderly, D=Drugs or alcohol).
The 95% confidence interval of the difference in means was estimated according to Rumsey (10). The 95% CI of the difference in two medians were estimated using bootstrapping techniques with 1000 replications (11).
*p value was calculated by between-groups comparison using student t-test and chi square/Fisher's exact test for continuous and categorical variables where appropriate.

respectively [11].

To identify risk factors for developing POAF, we used multivariate logistic regression with independent variables including age, gender, and comorbidities. Candidate variables including those which are significant in univariate analysis ($p<0.25$). Backward elimination was applied until only significant variables with $p<0.05$ remained in the model. Results are reported as frequency and percentages for incidences of events, odd ratio (OR) and 95% confidence intervals (CI) for logistic

Table 2: Risk factor associated with the occurrence of new-onset post-operative atrial fibrillation

Characteristics	Univariate logistic regression		Multivariate logistic regression	
	OR (95% CI)	P value	aOR (95% CI)	P value
Age	1.03 (1.00 – 1.06)	0.076		
Age group				
<65 years old (reference group)				
≥65 years old	3.80 (1.34 – 10.80)	0.012	3.78 (1.16 – 12.34)	0.028
Female gender	1.47 (0.69 – 3.11)	0.318		
BMI	0.99 (0.88 – 1.11)	0.865		
Type of surgery				
Coronary artery surgery (reference group)				
Non-coronary surgery	0.71 (0.20 – 2.58)	0.604		
Cardiac comorbidities				
Hypertension	1.25 (0.51 – 3.04)	0.627		
Vascular disease	2.44 (0.82 – 7.25)	0.110	1.88 (0.56 – 6.30)	0.305
Coronary artery disease	0.91 (0.27 – 3.05)	0.878		
Heart failure	1.80 (0.62 – 5.24)	0.281		
Non-cardiac comorbidities				
Diabetes	2.79 (0.66 – 11.78)	0.163	2.06 (0.42 – 10.09)	0.371
History of stroke	2.70 (0.24 – 30.64)	0.424		
Renal failure	1.63 (0.76 – 3.52)	0.213	0.95 (0.38 – 2.36)	0.912
Chronic hepatitis	NA	NA		
Chronic lung disease	1.30 (0.18 – 9.56)	0.798		
Thyroid disease	0.64 (0.06 – 7.22)	0.715		
Pre-operative echocardiography				
Left ventricular ejection fraction	1.00 (0.97 – 1.04)	0.869		
Left ventricular diameter	1.01 (0.98 – 1.05)	0.452		
Left atrial diameter	1.02 (0.98 – 1.07)	0.299		

Footnote: OR=odd ratio, aOR=adjusted odd ratio, CI=confidence interval, NA=not applicable.

regression. All analyses were performed using Stata version 16.0. A p value of <0.05 with two-tailed analysis is considered statistically significant.

Results

Baseline characteristics

Between August 2018 and December 2019, 337 patients underwent coronary and/or valvular surgery in our centre. Among these patients, 113met the selection criteria and provided informed consent, as indicated in the study flow diagram (Figure 3). After surgery, one patient developed complete heart block requiring pacing and was excluded from the study, resulting in a final sample size of 112 patients. Participant baseline characteristics are summarised in Table 1. The mean age of participants was 52.9±12.2 years, 50.9% were females and the median total length of stay was 22.0 days (IQR: 18.0-29.0days). Most patients underwent valvular surgery (n=103, 92.0%) with only 9.8%(n=11) undergoing CABG. Participants had a wide range of cardiac comorbidities including hypertension (n=25, 22.3%), heart failure (n=16, 14.3%), and non-cardiac comorbidities such as diabetes (n=9, 8.0%) and renal failure(n=43, 38.4%). The median CHA_2DS_2-VASc score was 1 (IQR:0to2), and median HASBLED score was 0 (IQR: 0 to 1). Among patients undergoing valvular surgery, 18 patients underwent valve repair, 34 received bioprosthetic valve, 30 received mechanical valve, and 21 patients underwent aortic valve reconstruction surgery using autologous pericardium. The mean left ventricular ejection fraction was 63.2%, mean left ventricular diameter was 53.0 mm, and mean left atrial diameter was 42.3 mm.

Incidence of POAF

New-onset POAF occurred in 43.8% (n=49) of participants post-surgery. The median time to first occurrence of new-onset POAF was 1.27 days (IQR 0.96 – 2.0 days) (Figure 4). Almost all episodes (48/49 patients, 98.0%) were captured in the ICU by using AliveCorKardia Device. The remaining one case was identified on the Thoracic and Cardiovascular Surgery ward.

Most patients with POAF (46/49, 93.9%) were consulted by a cardiologist. The primary treatment for POAF was antiarrhythmic

Figure 2: Microlife BP200 Afib.

Reused from Ngo et al[6].

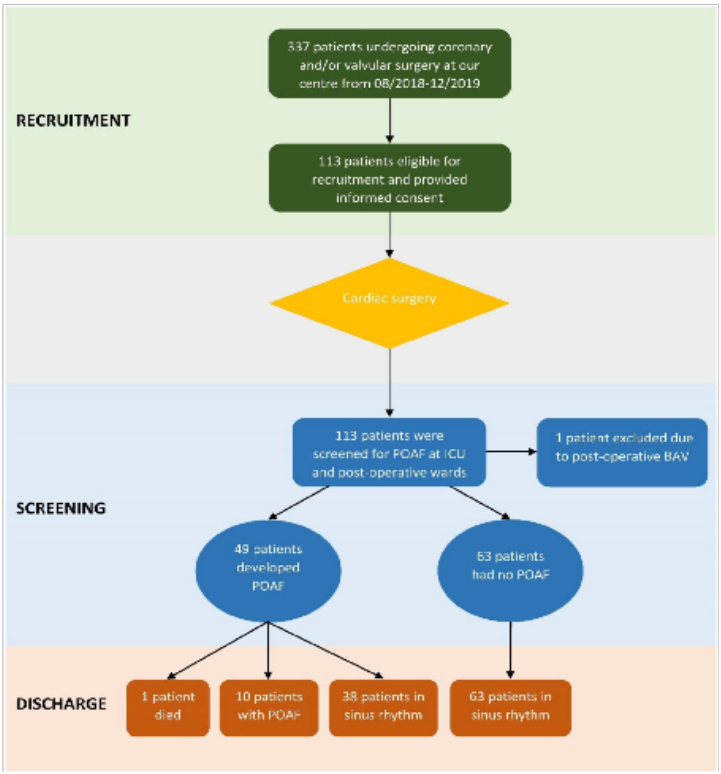

Figure 3: **Study flow chart.**

Adapted from Ngo et al [6]

drugs (amiodarone n=24; digoxin n=3). At discharge, 79.6% (39/49) of POAF cases converted to sinus rhythm, mainly with the use of anti-arrhythmic medications while 13 cases having spontaneously conversion. The other 20.4% (10/49) of patients remained in AF, of whom 7 had undergone bioprosthetic valve replacement, 2 received mechanical valves, and 1 valve repair surgery.

Risk factors

Patients with POAF had higher proportion of the older age group (≥65 years old, 28.6% vs. 9.5%, p=0.009). Rates of other comorbidities were comparable between patients who experienced POAF and who did not. Similar, median CHA_2DS_2-VASc (1.0 vs. 1.0, p=0.155) and HASBLED (0.0 vs.0.0, p=0.201) were comparable between groups. When different types of surgery were considered, incidences of POAF were comparable among patients underwent coronary artery surgery and valve surgery (36.4% vs. 44.6%, p=0.753).

Variables considered for logistic regression included age group (OR 3.68, 95% CI 1.30 – 10.49, p=0.014), vascular disease (OR 2.38, 95% CI 0.80 – 7.06, p=0.120), diabetes (OR 2.73, 95% CI 0.65 – 11.50, p=0.172), renal failure (OR 1.57, 95% CI 0.73 – 3.38, p=0.247), and left atrial diameter (OR 1.03, 95% CI 0.98 – 1.07, p=0.247) (Table 2). After logistic regression, we found that older age (≥65 years old) was the only factor significantly associated with an increased risk of developing POAF (adjusted OR 4.53, 95% CI 1.34 – 15.38, p=0.015).

Postoperative complications

Patients with POAF spent significantly longer time in the ICU (6.0 vs. 3.0 days, difference in medians: 3 days [95%CI 1.3-4.7], p<0.001) and in-hospital post-surgery (15.0 vs. 11.0 days, difference in medias: 4 days [95%CI 1.5-6.5], p=0.002) compared with those without POAF. POAF patients also had higher rates of major complications (26.0% vs 3.2%, p <0.001) which was driven by higher rate of pulmonary oedema (12.0% vs. 0.0%, p=0.006) (Table 3). Rates of death (4.0% vs. 0.0%, p=0.194), stroke (2.0% vs. 0.0%, p =0.442), major bleeding (8.0% vs. 1.6%, p=0.169), sepsis (4.0% vs 0.0%, p=0.194), delirium (14.0% vs. 6.4%, p=0.211) and pleural effusion (6.0% vs. 1.6%, p=0.320) were all higher in the POAF group although the differences did not reach statistical significance.

Feasibility of POAF screening strategy

Overall, the compliance rate was high and most of interviewees believed that this strategy could be implemented in the long-term, especially if regular training and Vietnamese translation are added.

Twelve staff including 5 doctors and 7 nurses completed the semi-structured interviews (Supplemental Appendix 1). All nurses who performed the POAF screening complied with the protocol. Most staffs reported the devices to be smaller, more convenient, quicker to be deployed, and provided results faster than the standard ECG recorder. They were supportive of screening for POAF, as they realised that the importance of POAF has not been adequately addressed in Vietnam. Almost all interviewees (11/12) thought that it may be possible to implement the POAF screening protocol in the long-term.

However, several difficulties were reported with the implementation of these devices. Firstly, both devices operate in English and not Vietnamese, which required prolonged time to follow the instructions and record the ECG, especially when errors happened. Secondly, the patients were mostly unconscious for several days post-surgery which significantly affected the patient-device contact and accordingly, quality of the recorded ECG. Therefore, it often took 15 minutes to record a 30-second single-lead ECG tracing with the Alive-Cor device (including time for patient preparation, repeated recordings due to low-quality ECG) while the Micro life device may take up to 5 minutes to measure blood pressure for 3 times consecutively. Consequently, staffs acknowledged that the POAF screening increased their usual workload moderately due to extra time needed to explain to the patients and record the ECG or measure blood pressure. Another interesting finding was that the quality of recording was significantly affected by the contact between the patient and the Alive CorKardia device given that the tracings were often collected in the postoperative setting on

Table 3: **Association of POAF occurrence and other postoperative complications.**

Complications	Overall cohort N=113	With POAF N=50	No POAF N=63	P value
Any major complication	14 (12.5%)	12 (24.5%)	2 (3.2%)	<0.001
Death	1 (0.9%)	1 (2.0%)	0 (0.0%)	0.437
Stroke	1 (0.9%)	1 (2.0%)	0 (0.0%)	0.437
Major bleeding	5 (4.5%)	4 (8.2%)	1 (1.6%)	0.166
Sepsis	1 (0.9%)	1 (2.0%)	0 (0.0%)	0.437
Pulmonary oedema	6 (5.4%)	6 (12.2%)	0 (0.0%)	0.006
Delirium	11 (9.8%)	7 (14.3%)	4 (6.4%)	0.206
Pleural effusion	4 (3.6%)	3 (6.1%)	1 (1.6%)	0.317

sedated patients. One nurse suggested that this could be resolved, at least in part, by applying 70-degree ethanol alcohol on the patient's fingers before recording.

The above issues were acknowledged to potentially impact the implementation and sustainability of the POAF screening strategy. Suggested solutions to overcome these hurdles and facilitate successful implementation of the POAF screening strategy include continuous training, and translation of the Alive CorKarida Device into Vietnamese. Specifically, the interviewees suggested that a monthly training session on how to recognize POAF on ECG tracing, how to use these devices, in addition to Vietnamese translation of the instructions could significantly facilitate the long-term implementation of such POAF screening strategy. They also suggested that the identification of new-onset POAF could be improved by using a telemetry system in the ICU that has the capacity to store all ECG recordings that could be reviewed later.

Discussion

In this first-ever POAF screening study in Vietnam, we found that the novel POAF screening strategy was feasible and detected a POAF incidence of 43.8%. The only risk factor for developing POAF identified in our study was older age (≥65 years old). The occurrence of POAF is associated with significantly prolonged ICU and post-operative length of stay, as well as higher risk of post-surgical pulmonary oedema. Staffs who were involved in this study showed good compliance with study protocol and provided important insights to its future implementation. Collectively, these findings suggest that the novel POAF screening strategy is feasible in a limited-resources-setting and provide some exploratory data regarding POAF in Vietnam.

AF newly develops after cardiac surgery has long been recognised as an important complication due to its high incidence as well as the worse surgical outcomes associated with this condition[2]. In Vietnam, however, little is known about this devastating disorder, in part due to the lack of equipment like telemetry as well as the shortages of staffs who already have a high workload. Consequently, there is a lack of awareness of POAF and strategies to prevent it. This study demonstrated that our novel POAF screening strategy is feasible as it is simple, uses devices that require minimal training and is integrated into the normal workflow so it does not significantly increase workload for staff(6). This is in line with two other recent studies that also demonstrated the feasibility of using these devices in low-resource settings in the community in both India [12] and Thailand [13]. Importantly, the semi-structure interviews provided important insights into the potential long-term implementation of this novel POAF screening strategy, identifying suggestions for improvement such as additional training and the need for translation of the devices into Vietnamese. Furthermore, as the majority of POAF cases were identified in the ICU, the potential use of telemetry that has the capability to store ECGs, could be a long-term solution to POAF screening, however the cost of this equipment would need to be considered.

Our study has provided the first preliminary data of POAF in Vietnam. Incidence of POAF in this study (43.8%) falls in the centre of the range reported in the literature(10-80%) [2,14-16]. However, this rate is much higher than the 3.9% reported among elderly patients admitted to the National Geriatrics Hospital in Vietnam[3], suggesting that POAF is not a trivial event which occurs with much higher incidence compared with that in the general population. Our study identified age ≥65 years as arisk factor of POAF and showed that the occurrence of this arrhythmia was associated with prolonged length of stay and higher risk of postoperative complications, which are consistent with previous literature[1]. Encouragingly, most events were consulted with a cardiologist and that most of these patients were discharged on sinus rhythm. However, ten patients were still in atrial fibrillation at discharge, of which seven had a bioprosthetic valve that may require long-term anticoagulation beyond the typically recommended three-month period [17]. Collectively, our findings confirm that in Vietnam, new-onset AF also had high incidence and associated with worse outcomes for patients undergoing cardiac surgery.

Some practical implications could be drawn from our findings. Firstly, healthcare providers (e.g. physicians, surgeons, doctors and nurses) taking care of patients after cardiac surgery in Vietnam all need to be more aware of the risk of developing POAF after cardiovascular surgery given its high incidence and its association with higher risk of postoperative complications, as well as its long-term management. Secondly, although our study was not powered to identify causes of POAF, we found advanced age to be the only risk factor and efforts to prevent patients from developing POAF may need to focus more on this specific group of patients. There are several strategies that have been shown to be effective in reducing the incidence of new-onset AF. For example, a systematic review of eight randomised trial involving 1,060 patients reported that the use of vitamin C treatment was associated with a more than 50% reduction in rate of POAF [18]. Other possible therapies include beta-blocker[19], corticosteroid [20], and colchicine [21]. We also suggest that this POAF screening strategy should be implemented in other centres to provide a more comprehensive understanding about POAF after cardiovascular surgery in Vietnam. It could also be used for POAF screening with other surgeries, or to follow response to therapeutic interventions like beta blockers, amiodarone, or Cox-Maze procedure.

When interpreting our results, several limitations should be considered. This is only a single-centre experience with small sample size that has limited the statistical power of several comparisons. Nevertheless, it has provided foundation for future studies including

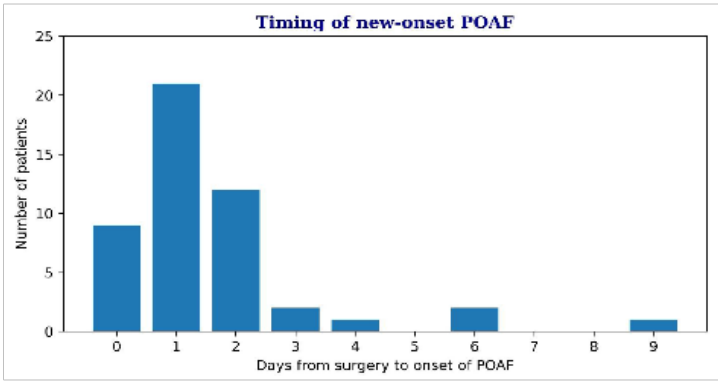

Figure 4: Timing of the onset of post-operative atrial fibrillation.

Abbreviation: POAF=post-operative atrial fibrillation.

those applying this POAF screening strategy in similar settings, or with other surgeries, or those using this strategy to follow-up response to treatment of POAF. The variable educational background and skills of the participating staffs in two different departments may have missed some cases and underestimated the true incidence of POAF.

Conclusions

In this single-centre study, using a novel POAF screening strategy, we found that 43.8% of patients undergoing cardiovascular surgery experienced new-onset POAF which was associated with higher risk of postoperative complications. Further studies using this strategy in other settings are encouraged, as well as to monitor response to therapeutic interventions.

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Click for Supplemental Appendix

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Effect of SLGT2 Inhibitors on Patients with Atrial Fibrillation

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Abstract

Background: Sodium glucose cotransporter 2 (SGLT2) inhibitors have been associated with various cardiovascular benefits. There is limited data examining the effect of these medications on atrial fibrillation (AF) associated clinical outcomes. We compared ischemic stroke, acute coronary syndrome (ACS), cardioversion, and all-cause mortality outcomes in AF patients on SGLT2 inhibitors to propensity matched controls.

Materials and Methods: We conducted a retrospective study with a global medical research network database. AF patients were identified via ICD codes that must have been present for at least one month. Patients on SGLT2 inhibitors were identified as those on dapagliflozin, empagliflozin, or canagliflozin for at least one month. AF patients on SGLT2 inhibitors were propensity matched to those not on SGLT2 inhibitors based on age, race, ethnicity, cardiovascular comorbidities, valvular disease, pulmonary disease, urinary diseases, cardiovascular procedures, cardiovascular medications, and anticoagulants. We examined incidence of ischemic stroke, at least one ACS episode, cardioversion, and all-cause mortality.

Results: In 26,269 AF patients, SGLT2 inhibitors were associated with lower risk of cardioversion (HR 0.921, 95% CI 0.841 - 0.999, p = 0.0245) and all-cause mortality (HR 0.676, 95% CI 0.635 - 0.721, p < 0.0001). However, there was an association with increased risk for ischemic stroke (HR 1.081, 95% CI 1.012 - 1.154, p 0.0201). There was no clear association with ACS events.

Conclusion: In patients with AF, use of SGLT2 inhibitors was associated with a lower risk of cardioversion and all-cause mortality and higher probability of survival based on Kaplan-Meier analysis.

Introduction

Diabetes mellitus (DM) is a major cardiovascular risk factor; it is associated with increased cardiovascular events, mortality, and hospitalization [1]. DM is also an independent risk factor for atrial fibrillation (AF) [2]. It is associated with increase AF burden, lower quality of life, and worse AF associated morbidities [3-5]. While the pathophysiologyis not fully understood, it is thought to be due to hyperglycemic-induced myocardial remodeling and expansion of epicardial adipose tissue. This leads to inflammation-related cardiac fibrosis and changes in electrical conduction that may lead to AF [5,6]. Sodium glucose cotransporter 2 (SGLT2) inhibitors were developed to selectively inhibit these transporters, found exclusively in the proximal convoluted tubule of the kidneys, thereby preventing glucose reabsorption, increasing urinary glucose excretion, and decrease blood glucose levels [7]. Several trials, including the EMPA-REG OUTCOME [8], CANVAS [9], DECLARE-TIMI 58 [10], CREDENCE [11], DAPA-HF [12], and EMPEROR-Reduced [13] trials, have demonstrated various cardiovascular benefits of these medications. However, none of these trials formally evaluated SGLT2 inhibitor effects on atrial fibrillation.

A post-hoc analysis of the EMPA-REG OUTCOME trial found that in patients with type 2 DM and established cardiovascular disease, irrespective of AF presence, empagliflozin reduced heart failure (HF) related hospitalizations and renal events [14]. With regards to SGLT2 inhibitor direct effects on AF, a post-hoc analysis of the DECLARE-TIMI 58 trial found that dapagliflozin reduced incidence of AF and atrial flutter related events regardless of prior history of AF or atrial flutter in type 2 DM patients [15]. Recently, analysis of the CREDENCE trial examined the effect of canagliflozin on stroke and AF in type 2 DM patients with diabetic kidney disease [16]. This analysis found no significant effect of canagliflozin on risk of hemorrhagic stroke, total stroke, and AF. However, the study was not powered to evaluate this specific effect. A meta-analysis of 16 trials found that SGLT2 inhibitors in patients with type 2 DM may reduce atrial fibrillation and atrial flutter as well as all-cause mortality [17]. Currently, there has been no study examining the direct effect of SGLT2 inhibitors on atrial fibrillation related outcomes and complications, regardless of diabetes status.

Therefore, we utilized a large medical research database to explore the effect of SGLT2 inhibitors on atrial fibrillation related outcomes

Key Words

Atrial Fibrillation; SGLT2 Inhibitors; Outcomes

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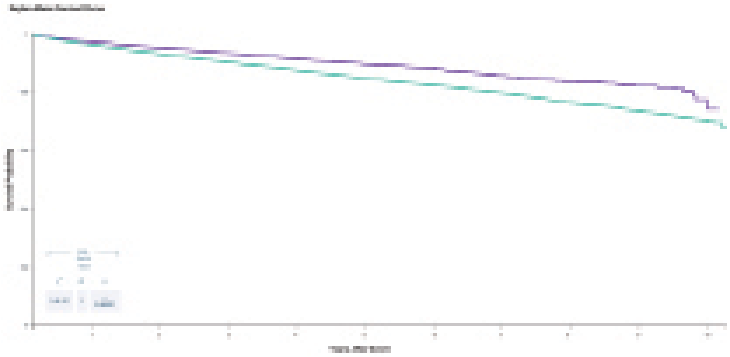

Figure 1: **Kaplan-Meier Survival Curve for AF Patients With and Without SGLT2 Inhibitors.**

Purple = Atrial Fibrillation patients with SGLT2 Inhibitors
Green = Atrial Fibrillation patients without SGLT2 Inhibitors

including stroke, acute coronary syndromes, cardioversion, and all-cause mortality in patients with atrial fibrillation. The goal of our study was to compare these outcomes in AF patients on SGLT2 inhibitors to propensity score matched patients with AF not on SGLT2 inhibitors.

Materials and Methods

Data Availability Statement

TriNetX global research network contains aggregate de-identified data from anonymously participating Healthcare Organizations (HCOs), mainly in the United States, but also throughout the world. TriNetX is compliant with the Health Insurance Portability and Accountability Act (HIPAA) and data displayed are in aggregate form, containing only de-identified data. Data can be accessed via TriNetX research network at https://live.trinetx.com. There may be costs and agreement forms needed to obtain data.

Patient Database

TriNetX (Cambridge, MA) is a global health research network with access to electronic medical records, including diagnoses, procedures, medications, laboratory values, and genomic information from 53 health care organizations (academic medical centers, physician practices, and community hospitals) with approximately 63,500,569 patients greater than or equal to 18 years old as of August 18, 2021. It is compliant with HIPAA, the US federal law which protects the privacy and security of healthcare data. Any data displayed on the TriNetX Platform in aggregate form, or any patient level data provided in a data set, only contains de-identified data as per the de-identification standard defined in HIPAA Privacy Rule.

Study Design

This is a retrospective observational study conducted via data from TriNetX Research Network. Inclusion criteria was: (1) patients having atrial fibrillation (AF) based on the International Classification of Diseases (ICD), Ninth and Tenth Revisions, Clinical Modification codes (I48.91, I48.0, I48.2, I48.1, I48.20, I48.19, I48.21, I48.11, I48.9, I48.21, I48.11) that was (2) present for at least one month. For the SGLT2 inhibitor cohort, we included (3) patients on SGLT2 inhibitors empagliflozin, dapagliflozin, or canagliflozin and (4) were on the medication for at least one month. These three were chosen due to being the most studied medications. The control cohort was designated as AF patients that were not on empagliflozin, dapagliflozin, or canagliflozin. We excluded patients that had a diagnosis of atrial flutter.

Outcomes were based on ICD codes and Common Procedure Coding System (CPT) codes that occurred at least one month after the diagnosis of AF with SGLT2 inhibitors or AF without SGLT2 inhibitors. Outcomes included ischemic stroke (I63, I63.50, G46.4, G46.3, I63.40, I63.239, I63.30, I63.139, I66.09, I63.139, I66.09, I63.59, I63.22, I63.219, I63.019, I63.20), acute coronary syndrome including unstable angina, non-ST elevation myocardial infarction, and ST elevation myocardial infarction (I20.0, I21.3, I21.1, I21.0, I21.19, I21.09, I21.2, I21.29, I21.11, I21.02, I21.21, I21.01, I21, I21.4, I25.110, I25.710, I25.700, I25.720, I25.790, I25.750, I25.760, I25.730), cardioversion (250980009, 5A2204Z, 1012978, 92960, 92961), and all-cause mortality.

Data Collection

TriNetX was accessed on August 18, 2021, and an anonymous data set from January 1, 2016, to August 18, 2021, was obtained. SGLT2 inhibitor cohort consisted of all patients greater than or equal to 18 years old with the diagnosis of AF, based on ICD codes above, and on either empagliflozin, dapagliflozin, or canagliflozin for at least 30 days. The control cohort was composed of all patients greater than or equal to 18 years old with the diagnosis of AF and not on empagliflozin, dapagliflozin, or canagliflozin. 48 participating healthcare organizations had data available for this patient population. Afterwards, propensity-scored matching was conducted and outcomes were collected.

Statistical Analysis

Statistical analysis was conducted via the TriNetX online platform. Categorical variables were compared utilizing chi-square tests and continuous variables were compared utilizing independent sample t-tests. Propensity score matching at a 1:1 ratio was conducted with logistic regression to control for current age, age at AF diagnosis, gender, race, ethnicity, hypertensive diseases, hypertensive heart disease, ischemic heart disease, heart failure, valvular heart disease, metabolic syndrome (including, but not limited to hyperlipidemia, obesity, and overweight), type 2 diabetes mellitus, cerebrovascular disease, chronic kidney disease, respiratory disease, nervous system disease, neoplasms, disease of the urinary tract, cardiovascular procedures (including but not limited to echocardiography, cardiac catheterization, revascularization, coronary artery bypass grafts), cardiovascular medications (including, but not limited to: beta blockers, calcium channel blockers, antiarrhythmic drugs, antianginals), and anticoagulants (including, but not limited to: direct oral anticoagulants, warfarin, and heparin).

Cox proportioned hazards ratio with 95% confidence intervals (CI) for incidence of stroke, acute coronary syndrome (ACS), cardioversion, and all-cause mortality were generated after propensity score matching. Kaplan-Meier analysis was conducted to estimate all-cause mortality. Statistical significance was set at $p < 0.05$.

Results

Baseline Characteristics

A total of 48 HCOs provided data for patients with AF on SGLT2

Table 1: Baseline Characteristics of the AF Patients With and Without SGLT2 Inhibitors Before and AfterPropensity-Score Matching

	Initial Populations			Propensity Score Matched Populations		
	AF and SGLT2i (n=26,294)	AF and No SGLT2i (n=1,368,518)	P-Value	AF and SGLT2 (n=26,269)	AF and No SGLT2 (n=26,269)	P-Value
Age (years) at Dx of AF (mean + SD)	66.2 + 10.5	71.3 + 12.9	< 0.0001	66.3 + 10.5	64.2 + 12.7	< 0.0001
Gender						
Male	68.5%	56.1%	< 0.0001	68.5%	70.7%	< 0.0001
Female	29.9%	43.4%	< 0.0001	29.9%	28.0%	< 0.0001
Unknown	1.5%	0.5%	< 0.0001	1.5%	1.3%	0.0347
Race/Ethnicity						
White	75.6%	79.6%	< 0.0001	75.7%	76.9%	0.0004
Black	12.5%	8.7%	< 0.0001	12.5%	11.9%	0.0809
Asian	1.3%	1.4%	0.6303	1.3%	1.2%	0.3536
Hispanic/Latino	4.9%	3.2%	< 0.0001	4.8%	4.6%	0.1878
Co-Morbidities						
HTN	80.5%	43.5%	< 0.0001	80.5%	78.3%	< 0.0001
Ischemic Heart Disease	54.4%	22.8%	< 0.0001	54.4%	53.4%	0.0177
Heart Failure	43.4%	15.1%	< 0.0001	43.4%	41.8%	0.0002
Metabolic Diseases	77.6%	39.3%	< 0.0001	77.6%	75.4%	< 0.0001
Nonrheumatic Mitral Valvular Disease	20.8%	8.8%	< 0.0001	20.8%	19.7%	0.0015
Nonrheumatic Aortic Valve Disease	13.8%	7.3%	< 0.0001	13.8%	12.6%	< 0.0001
Chronic Rheumatic Heart Disease	13.5%	5.7%	< 0.0001	13.5%	12.6%	0.0013
Type 2 Diabetes Mellitus	77.7%	17.4%	< 0.0001	77.7%	77.7%	0.8421
Cerebrovascular Disease	21.2%	11.7%	< 0.0001	21.2%	19.9%	0.0003
Chronic Kidney Disease	25.2%	11.4%	< 0.0001	25.2%	23.9%	0.0004
Respiratory Disease	58.1%	32.2%	< 0.0001	58.1%	56.2%	< 0.0001
Nervous System Disease	61.3%	32.1%	< 0.0001	61.3%	59.95%	0.0017
Neoplasms	34.1%	21.9%	< 0.0001	34.1%	33.1%	0.0114
Others						
Cardiovascular Procedures	67.7%	39.5%	< 0.0001	67.7%	66.0%	< 0.0001
Cardiovascular Medications	91.7%	57.0%	< 0.0001	91.7%	91.7%	0.8867
Anticoagulants	73.2%	36.1%	< 0.0001	73.2%	73.6%	0.2731

AF = Atrial Fibrillation, SGLT2i = Sodium-Glucose Co-Transporter 2 inhibitor, Dx = Diagnosis, SD = Standard Deviation, HTN = Hypertension

inhibitors and not on SGLT2 inhibitors. There were 26,294 patients with AF and an SGLT2 inhibitor and 1,368,518 patients with AF and not on an SGLT2 inhibitor. After propensity score matching, both cohorts had a size of 26,269 patients (Table 1). The average age at the diagnosis of atrial fibrillation for patients in the SGLT2 inhibitor cohort and no SGLT2 inhibitor group was 66.3 + 10.5 years and 64.2 + 12.7 years respectively. The majority in each cohort were of male gender (68.5% and 70.7% respectively). 80% of patients in both cohorts had hypertension, approximately 79% had type 2 diabetes mellitus, 77% had metabolic diseases, 61% had nervous system diseases, and 57% had respiratory system diseases. Approximately 92% were on cardiovascular medications and 73% were on anticoagulants (Table 2).

Outcomes

In the cohorts of 26,269 AF patients, SGLT2 inhibitors were associated with a higher risk of ischemic stroke (HR 1.081, 95% CI 1.012 – 1.154, p 0.0201) based on Cox Proportioned Hazards Model. SGLT2 inhibitors were associated with a higher risk of acute coronary syndrome (HR 1.04, 95% CI 0.99 – 1.10, p 0.1458), although this did not reach statistical significance. AF patients on SGLT2 inhibitors were also associated with lower risk for cardioversion (HR 0.912, 95% CI 0.841 - 0.999, p 0.0248). Lastly, SGLT2 inhibitors in AF patients were associated with lower all-cause mortality (HR 0.676, 95% CI 0.635 - 0.721, p < 0.0001) (Table 3). Kaplan-Meier analysis demonstrated survival probability was higher in patients with AF and SGLT2 inhibitors (74.1% vs. 67.6%, p < 0.0001) (Figure 1).

Discussion

This is the first observational study to examine the effect of SGLT2 inhibitors and outcomes on patients with atrial fibrillation. The main findings of this study show that patients with AF on these medications were associated with lower risk of cardioversion and all-cause mortality. There appears to be a higher tendency toward an ischemic stroke and acute coronary syndrome.

Ischemic Stroke

Atrial fibrillation is associated with increased risk of stroke, systolic embolism, and death [18,19]. Currently, the CHADS2VASc score has

Table 2: Cardiovascular Medications in Atrial Fibrillation Patients With and Without SGLT2 Inhibitors Before Propensity Matching

Medications	AF and SGLT2i (n=26,294)	AF and No SGLT2i (n=1,368,518)
Cardiovascular Medications	92%	63%
Antilipemic Agents	78%	38%
Atorvastatin	55%	23%
Simvastatin	19%	12%
Rosuvastatin	18%	6%
Pravastatin	13%	6%
Fenofibrate	9%	2%
Ezetimibe	8%	3%
Beta Blockers/ Related	77%	43%
Metoprolol	57%	30%
Carvedilol	27%	9%
Labetalol	12%	6%
Diuretics	68%	35%
Loop Diuretics	54%	24%
Thiazides	36%	18%
Potassium Sparing Diuretics	27%	8%
ACE Inhibitors	52%	24%
Lisinopril	43%	20%
Enalapril	4%	2%
Benazepril	3%	2%
Calcium Channel Blockers	47%	27%
Amlodipine	28%	17%
Diltiazem	18%	9%
Verapamil	9%	3%
Nifedipine	3%	2%
Angiotensin II Inhibitors	42%	15%
Antianginals	35%	14%
Nitroglycerin	30%	12%
Isosorbide	11%	4%
Isosorbide Dinitrate	5%	1%
Ranolazine	3%	1%

AF = Atrial Fibrillation, SGLT2i = Sodium-Glucose Co-Transporter 2 inhibitor, ACE = Angiotensin Converting Enzyme

been utilized to assess risk of stroke in AF patients [20,21]. Diabetes mellitus is one of the risk factors that is associated with a 2-fold risk of stroke alone [22]. SGLT2 inhibitors in diabetic patients has to been evaluated and found to have no significant differences in stroke risk from previous meta-analysis of 32 trials [23]. A recent post-hoc analysis of 142 patients from the CREDENCE trial found that there was no clear effect of SGLT2 inhibitors on stroke risk in patients with AF and diabetic kidney disease, but the study was not powered to assess this outcome [24]. Our study shows AF patients on SGLT2 inhibitors may be associated with a higher risk of ischemic stroke and appears to agree with the previous study. There have been previous data demonstrating glucose-lowering agents have limited effect on stroke prevention [35]. In previous studies, empagliflozin has been associated with systolic blood pressure reduction and hemoconcentration that may increase the risk for ischemic stroke [36]. Further data will be needed to examine this association and relationship.

The most likely hypothesis for the increased risk of ischemic stroke is the blood pressure lowering effect associated with SGLT2 inhibitors. Lower blood pressure poses a risk for hypovolemia and hypotension leading to hypoperfusion and ischemic stroke. The major mechanism for this blood pressure effect may be related to natriuresis, osmotic diuresis, and reduction in body weight [37,38]

Acute Coronary Syndrome

There have been multiple trials with results on major adverse cardiovascular events, including myocardial infarction (MI). The EMPA-REG OUTCOME trial demonstrated 14% relative risk reduction in major adverse cardiovascular events (MACE) including MI [8]. Specifically for myocardial infarction, there was no statistically significant difference in findings. The CANVAS trial demonstrated 14% relative risk reduction of a major adverse cardiovascular event but also demonstrated no statistically significant difference in MI events [9,32]. Similarly, the CREDENCE trial demonstrated a relative risk reduction in cardiovascular death, MI, or stroke [11]. The DECLARE-TIMI 58 provided the largest trial and still found a non-statistically significant risk reduction in MACE, including MI [15]. Our study demonstrated a non-significant association of SGLT2 inhibitors and ACS events in patients with atrial fibrillation. Again, this may be related to diabetic related microvascular disease. Currently, SGLT2 inhibitors have been thought to have anti-atherosclerotic effects through glucose control, blood pressure control, and weight loss [39]. However, patients on SGLT2 inhibitors may have already worsened diabetic microvascular disease that may be confounding the outcome of ACS events. Further trials will be needed to examine the association with ACS events and SGLT2 inhibitors.

Cardioversion

Currently, direct-current cardioversion is a Class 1 recommendation for pursuing rhythm-control strategies for AF patients [33]. The findings of this study present that AF patients taking SLGT2 inhibitors are associated with lower risk of cardioversion compared to AF patients not taking these medications (HR 0.921, 95% CI 0.841 - 0.999, p = 0.0245). Therefore, this study presents new data that SGLT2 inhibitors are associated with lower risk for cardioversion and may affect the morbidity of AF patients. Further data should be explored to closely examine the association and relationship.

With regards to mechanism, there are currently animal models that have found SGLT2 inhibitors to suppress inflammation and oxidative stress in diabetic rodents [40]. A hypothesis is that this decreases inflammation and myocardial fibrosis. This decrease in fibrosis can lead to less alterationin the electrical properties of the atrial tissue and could be a possible explanation for the associated lower risk for cardioversion.

All-Cause Mortality

SGLT2 inhibitors have been associated with lower cardiovascular mortality in various patient populations including diabetes, chronic kidney disease, and heart failure [8-13]. Similarly, our study demonstrated that SGLT2 inhibitors are associated with lower mortality in AF patients (HR 0.676, 95% CI 0.635 - 0.721, p < 0.0001) compared to those not on them. This provides further evidence that supports previous studies, including a meta-analysis demonstrating an association of SGLT2 inhibitors with lower risk of sudden cardiac death [33].

Table 3: Outcomes of AF Patients With and Without SGLT2 Inhibitors After Propensity-Score Matching

	HR	95% CI	P-Value
Ischemic Stroke	1.08	1.01 – 1.15	0.0201
ACS	1.04	0.99 – 1.10	0.1458
Cardioversion	0.91	0.84 – 0.99	0.0248
Mortality	0.68	0.64 – 0.72	< 0.0001

HR = Hazards Ratio, CI = Confidence Interval, ACS = Acute Coronary Syndrome

There are multiple hypotheses as to the overall mortality benefit in cardiovascular patients. SGLT2 inhibitors have been associated with lower blood pressure, increased diuresis, improved cardiac energy metabolism, decreased inflammation, weight loss, improved glucose control, improved cardiac remodeling, preventing ischemic myocardial injury, decreased epicardial fat, and decreased oxidative stress [41]. These effects are likely to extend to atrial fibrillation patients, who are also likely to have many similar cardiovascular morbidities that SGLT2 inhibitors are known to impact. In addition, SGLT2 inhibitors may affect left atrial appendage (LAA) remodeling either directly, by reducing cardiac remodeling, or indirectly, by lowing blood pressure and in turn LAA pressure. Further studies are needed to explain the mechanism of SGLT2 inhibitors impact on atrial fibrillation related mortality.

Limitations

Aside from the inherent limitation of retrospective analysis there are several other limitations to this study. First, these results are based on aggregate data of ICD and CPT codes. There is a possibility of underreporting patients due to timing and number of diagnosis codes as well as CPT codes. We attempted to address these issues by utilizing time constraints when possible. For example, we included only patients with ICD codes for atrial fibrillation that was present for at least one month. Similarly, we only included patients that were on SGLT2 inhibitors for at least one month. This also limited the evaluation of cardiovascular specific mortality as there is no specific code for that. Second, when utilizing the TriNetX data platform, we are limited to use the platform analytical power and limiting us to their calculations and methods. Thirdly, we were unable to directly compare dapagliflozin, canagliflozin, and empagliflozin due to the limitation of the analytical software. Another limitation of this study was the inability to account for socioeconomic status (SES) risk factors in atrial fibrillation. It has been established that SES plays a role in AF burden [34] and plays a role in access to SGLT2 inhibitors. Despite these limitations, and with a comprehensive propensity score matching to any possible confounding factors, this study does provide evidence of the benefit of SGLT2 inhibitors in AF patients, and it should pave the way for prospective trials to provide further proof of this association.

Conclusion

In 26,269 patients with atrial fibrillation, use of SGLT2 inhibitors was associated with lower risk of all-cause mortality. This study provides further evidence for the benefits of SGLT2 inhibitors in patients with atrial fibrillation. Further data should be examined prior to determination of the full effect of SGLT2 inhibitors for this patient population.

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Same Day versus Overnight Discharge in Patients Undergoing Ablation for Atrial Fibrillation (SODA) Study

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Abstract

Patients undergoing catheter ablation for atrial fibrillation (AF) are routinely admitted for observation overnight in the hospital. With the rising incidence of AF among the population, increased volumes of procedures are placing increased demands on hospital resources. The purpose of this study was to evaluate the efficacy and safety of same day discharge in patients undergoing ablation for AF when compared to patients admitted for overnight observation. We performed a retrospective analysis using a multicenter cohort among patients who were discharged home after elective pulmonary vein isolation (PVI) ablation for AF. In our analysis, we found no statistically significant difference between patients discharged on the day of their procedure when compared to patients admitted for overnight observation in terms of 90-day readmission, major adverse cardiovascular events and death. This study shows that same day discharge after AF ablation is a feasible option. Future studies are needed to elicit the appropriate protocol to use.

Introduction

Atrial Fibrillation (AF) is the most commonly diagnosed cardiac arrhythmia, with an estimated 6.1 million cases in the United States and is expected to double by 2030 [1]. Catheter ablation for AF is a common procedure performed to scar or eliminate the triggers that cause AF. It is an effective treatment and has been shown to be superior to antiarrhythmic therapy in patients with symptomatic AF. With continued advancement in pulmonary vein (PV) ablation, procedural outcomes have seen tremendous improvement while complications have gone down significantly. These factors have led to an increased number of AF ablation procedures being performed [2-4].

It is common practice and expert medical consensus to keep patients overnight in the hospital after an AF ablation procedure. However, the inpatient costs are extremely high and the increased number of procedures being performed place increased demand on the healthcare system [5]. Furthermore, the emergence of the COVID-19 pandemic has greatly affected health care delivery worldwide. A massive reallocation of health care resources has created major obstacles to routine medical care in addition to the need to limit disease transmission as infected patients fill hospital beds. As a result, research is being done to evaluate more cost-efficient models of post-ablation care without compromising the quality of the current practice or risking further complications in patients. This has led to research being performed on the efficacy and safety of early or same-day discharge after AF ablation. Research has already been performed showing same-day discharge is safe and effective for less complex ablations such as atrial flutter. AF ablation is generally a more complex procedure with longer sedation times and higher levels of anticoagulation [6-7].

The purpose of this study is to examine the potential relationship between patients undergoing AF ablation being discharged on the same day versus the standard overnight hospital admission.

Key Words

Atrial Fibrillation, Pulmonary Vein Isolation, Same Day Discharge.

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Methods

Data Collection

This is a retrospective multicenter cohort study among patients who were discharged home after elective pulmonary vein isolation (PVI) ablation for AF at hospitals and surgical centers in the United States run by Hospital Corporations of America (HCA) between January 2015 and December 2018. All outpatient procedures in adults over 18 years of age were included. Patients who were inpatient or were hospitalized over 48 hours were excluded.

Inclusion Criteria:
1. Age > 18 years
2. Outpatient PVI ablation
3. Hospital stay <48 hours.

Exclusion Criteria
1. An inpatient stay prior to the procedure

Table 1: Patient Encounters

	Number of Patient Encounters
Same-day discharge	1255
Overnight stay	12312
Total	13567

2. Hospital stay > 48 hours post-procedure.

Using the above-mentioned inclusion-exclusion criteria, patient encounters were pulled by data analysts using CPT codes for PVI ablation. Patient encounters that met the exclusion criteria were eliminated and resultant encounters were used for the study. 17,724 ablation procedures were pulled from HCA's electronic data warehouse. 14,290 of these patients underwent PVI ablation on the day they presented to the hospital. Admissions < 48hours were randomly selected from these patients leaving a patient population of 13,567 patients.

Patient data included patient demographics, date of admission, date of discharge and home medications. Limited medical history was obtained through ICD 10 codes. Readmission at 90 days was evaluated by reviewing the patient encounters and matching with the patient account number (e.g., if the same account number had a second encounter within 90 days after the date of the procedure, it qualifies for all-cause readmission). Principal and sub investigators were blinded and provided with de-identified data only [Table 1].

Data Analysis

The resultant data was entered into SPSS software for analysis. Logistic regression analysis was made to evaluate for 90-day readmission rates. Multiple logistic regression was performed for both 90-day all cause readmission and 90-day AF readmission. Variables included in the model are overnight status, age, sex, race (white/other), hypertension without CKD, hypertension with CKD, CHF, diabetes type II, anticoagulants, antiplatelets, rate control medications, and rhythm control medications.

Results

There was no statistically significant difference in mortality, major adverse cardiovascular events, 90-day all-cause readmission or 90-day AF readmissions. A logistic regression analysis was performed and found no statistically significant difference between patients who were admitted overnight when compared to patients discharged on the same day as their AF ablation in terms of 90-day all-cause readmission and 90-day AF readmission. In a subgroup analysis, there was a statistically significant decrease in 90-day all-cause readmission in patients discharged on rate lowering medications versus those who were not (p-value 0.005, OR 0.358, 95% CI 0.175-0.734) (Tables 2-4).

Discussion

AF is the most prevalent cardiac arrhythmia in clinical practice. The incidence and prevalence of AF are expected to increase drastically over the next decades, further increasing procedural volumes for AF ablation and hospital demand. Catheter ablation for AF is the most common ablation procedure and typically requires at least one overnight hospital stay [8-10]. The new burdens placed upon the healthcare industry by the COVID-19 pandemic have further compromised the delivery of these procedures for many institutions worldwide. Given the current state of the COVID-19 pandemic, many institutions have elected to reduce non-urgent procedures to preserve resources, reduce viral transmission and maximize hospital capacity. A model of same day discharge for patients undergoing ablation for atrial fibrillation may play an important role in the post-surge period as well as throughout seasonal pandemic fluctuations in the future.

Census projection estimated approximately three million individuals in the U.S. with a diagnosis of AF in 2020, with a projected increase to ~5.6 million people by 2050 [11]. With the growing number of diagnoses, AF ablation procedures have continued to rise with a decrease in complications. Thus far there is no standardized recommendation regarding discharge time after catheter ablation. Historically, the majority of centers have and many still admit patients for at least one overnight stay following AF ablation procedures [12-15]. A same day discharge approach can not only improve patient experience and satisfaction, but it can reduce the burden on our healthcare system and cut down on unnecessary healthcare costs.

There are a growing number of studies investigating same-day discharge. Deyell et al reported on over 3,000 patients at two centers in Canada undergoing same-day discharge for AF ablation. In their study, the primary reason for later discharge were access site problems, intraprocedural complications, late procedure times, and complications related to anesthesia [13-19]. Other studies have shown up to 80% of patients undergoing AF ablation may be amenable to same-day discharge if avoidable delays in care and complications had been anticipated. Many studies were conducted at single centers and have used protocols and patient selection when addressing same-day discharge [20-25]. Our study is unique in that it was conducted across multiple centers across the nation and no patient selection or protocols were implemented. Despite this, our results still showed no significant difference in mortality, MACE, or 90-day readmission in patients undergoing PVI ablation for AF when discharge on the same day as the procedure.

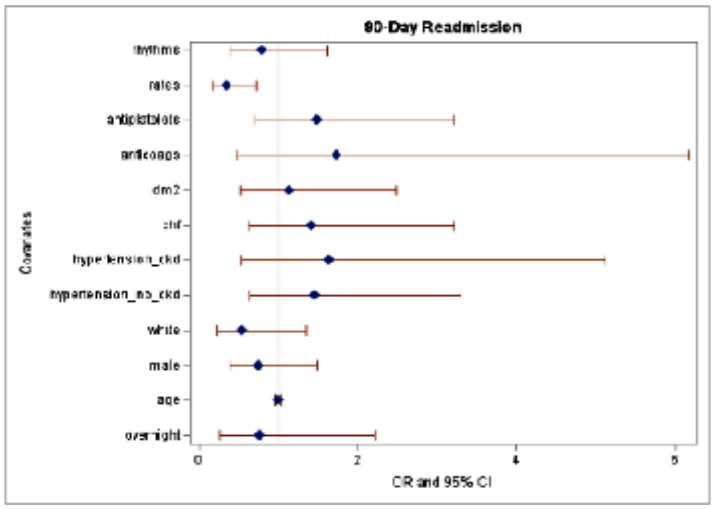
This retrospective multicenter cohort study among patients who were discharged home after elective PVI ablation for AF showed that same-day discharge was not associated with a statistically increased rate of morbidity, mortality, or 90-day readmission rates. In fact, our subgroup analysis showed that being on rate control medications may have a higher impact on readmission than same day discharge. We included this subgroup along with patients on rhythm control medications to be included in our logistical regression analysis to control for confounding variables. Interestingly, being on rate control and not rhythm control

Table 2: Patient Distribution

	Same-day discharge (N=1255)			Overnight Stay (N=12312)		
	Yes	No	%	Yes	No	%
Mortality	1	1254	0.08	4	12308	0.03
90-day all-cause readmission	5	1250	0.4	31	12281	0.25
90-day AFib readmission	5	1250	0.40	24	12288	0.20

Table 3: 90-day All-Cause Readmissions

	Adjusted Odds Ratio	95% CI	P-value
Overnight	0.771	0.266-2.238	0.633
Age	0.994	0.962-1.026	0.709
Male	0.754	0.385-1.477	0.411
HTN/no CKD	1.472	0.653-3.315	0.351
HTN/CKD	1.724	0.557-5.334	0.344
CHF	1.433	0.632-3.246	0.389
DM 2	1.178	0.539-2.577	0.682
Anticoagulant Medication	1.732	0.487-6.154	0.396
Anti-platelet Medication	1.472	0.684-3.167	0.322
Rate Control Therapy	0.358	0.175-0.734	0.005
Rhythm Control Therapy	0.805	0.398-1.629	0.545



was associated with a decrease in readmission rates.

Same day discharge after AF ablation has the potential to reduce healthcare utilization, increase patient satisfaction and lessen the cost per patient encounter. Delivering cost effective healthcare while not compromising the quality of care should be of utmost importance. This study should provide more data reassuring that same-day discharge is safe for the majority of patients undergoing AF ablation. Future research regarding the design of specific protocols and the optimal patient selection are needed.

Limitations

Discharging patients on the same day after the AF ablation procedure is not a common practice. Due to this, our study is limited to an unevenly low distribution of patients who were discharged on the same day. It also affected the distribution of patients based on various demographics. This is a multicenter study involving patient encounters in hospital settings and hospitals. Due to this, there are various confounding factors like operator skill, lab facility, post-operative care management, recognition of immediate complications and follow up care. Regarding decreased readmission in patients on rate control therapy, we included this subgroup along with patients on rhythm control medications to be included in our logistical regression analysis to control for confounding variables. Interestingly, being on rate control and not rhythm control was associated with a decrease in readmission rates. This may be because patients on rhythm control had more refractory or medication-resistant atrial fibrillation. The study was also not specifically powered to look at rate vs. rhythm control, so results should be interpreted with caution.

Conclusion

Our study adds to the growing amount of evidence pointing to the safety and efficacy of same day discharge in patients undergoing AF ablation. Further studies are warranted investigating factors that place patients at increased risk for adverse events at same day discharge.

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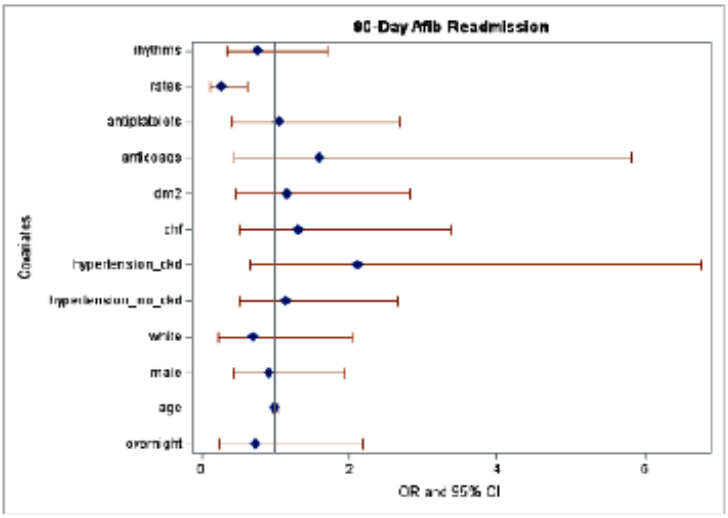
Table 4: 90- Day AF Readmission

	Adjusted Odds Ratio	95% CI	P-value
Overnight	0.736	0.248-2.183	0.58
Overnight	0.999	0.975-1.024	0.949
Male	0.91	0.427-1.94	0.807
HTN/no CKD	1.148	0.498-2.645	0.745
HTN/with CKD	2.171	0.684-6.894	0.188
CHF	1.323	0.515-3.398	0.56
DM 2	1.187	0.49-2.878	0.704
Anticoagulant Medication	1.602	0.441-5.819	0.474
Anti-platelet Medication	1.036	0.405-2.649	0.941
Rate Control Therapy	0.276	0.12-0.638	0.003
Rhythm Control Therapy	0.767	0.344-1.71	0.516



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Extensive Left Atrial Low-Voltage Area During Initial Ablation is Associated with A Poor Clinical Outcome Even Following Multiple Procedures

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Abstract

Background: Some patients fail to respond to persistent atrial fibrillation (PeAF) catheter ablation in spite of multiple procedures and ablation strategies, including low voltage area (LVA)-guided, linear, and complex fractionated atrial electrogram (CFAE)-guided ablation procedures. We hypothesized that LVA extent could predict non-responseto Pe AF catheter ablation in spite of multiple procedures.

Methods: This study included 510 patients undergoing initial ablation procedures for PeAF. LVAs were defined as regions with bipolar peak-to-peak voltages of <0.50 mV after PVI during sinus rhythm. Patients were categorized by LVA size into groups A(0-5 cm^2), B (5-20 cm^2), and C (over 20 cm^2). The primary endpoint was AF-free survival after the last procedure.

Results: During a median follow-up of 25 (17, 36) months, AF recurrence was observed in 101 (20%) patients after 1.4±0.6 ablation procedures (maximum 4). Comparison of clinical outcomes after multiple procedures in the three groups showed that the results depended on the extent of LVA. Multivariate analysis of AF-free survival after the last procedure showed that LVAs > 20 cm^2 was an independent factor associated with AF recurrence after the final procedure(Hazard ratio, 7.94; 95% confidence interval, 2.91 to 21.67, P <0.001).

Conclusions: Extensive LVA after initial PVI was associated with poor clinical benefit despite multiple catheter based ablations.

Introduction

Although catheter ablation has been established as an important treatment for atrial fibrillation (AF), the outcomes of PVI alone for persistent AF (PeAF) are unsatisfactory.[1-3] Substrate modification to improve outcomes has been performed, and favorable out comes have been reported for low voltage area (LVA)-guided, linear, and CFAE ablation.[4,5] Nevertheless, some patients remain as non-responders to PeAF catheter ablation in spite of multiple procedures and various ablation strategies. The prevalence of left atrial low-voltage areas (LVAs) is strongly associated with the recurrence of atrial tachyarrhythmias following catheter ablation.[6-11] We considered that LVA extent could predict non-responders to PeAF catheter ablation in spite of multiple procedures.

Key Words

Atrial Fibrillation, Catheter Ablation, Low Voltage Area, Multiple Procedures.

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Methods

Study subjects

From October 2014 to December 2018, 518 consecutive patients undergoing initial ablation for persistent AF using Carto 3 (Biosense Webster, Inc., Diamond Bar CA, USA), EnsiteNavX (St. Jude Medical, Inc., St. Paul MN, USA) or Rhythmia (Boston Scientific, Boston MA, USA) at our hospitalwere retrospectively enrolled. Persistent AF was defined as a sustained episode lasting ≥7 days at enrollment. Patients who could not undergo voltage mapping were excluded. Other exclusion criteria were age <20 years, left atrial thrombus, and prior catheter ablation of AF. This study complied with the Declaration of Helsinki. Written informed consent for ablation and the use of data in this study was obtained from all patients, and the protocol was approved by our institutional review board.

Catheter ablation procedure

We discontinued all antiarrhythmic drugs (AADs) ≥ 3 days before ablation, except for amiodarone, which was stopped ≥1 month before. Patients underwent transesophageal echocardiography (TEE) the day before the procedure to exclude the presence of thrombi.

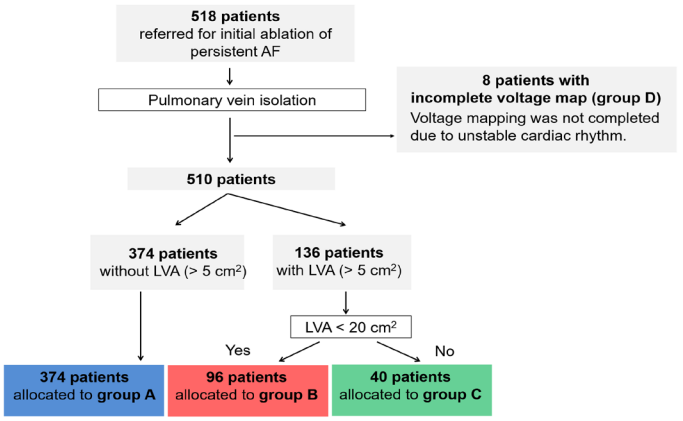

Figure 1: Patient flow chart.

Among 518 patients in whom voltage mapping was attempted, 374 patients had no LVA (group A). The remaining 136 patients had LVAs after PVI and were allocated to group B orC according to the size of the LVA. Voltage mapping was not completed in 8 patients (group D) due to unstable heart rhythm.

Electrophysiological studies and catheter ablation were performed under intravenous sedation with dexmedetomidine or propofol, with the latter performed by one of four experienced operators (M.M, T.K, A.S, and Y.M). Most of the patients underwent radiofrequency catheter ablation. Cryoballoon ablation was performed for persistent AF of short standing. Patients with common PVs or a large PV diameter underwent radiofrequency catheter ablation.

In cryoballoon ablation, an Arctic Front Advance cryoballoon catheter with a 28-mm balloon size (Medtronic, Inc., Minneapolis MN, USA) was passed into each PV under guidance by fluoroscopy and the 3-D mapping system. After confirming PV occlusion by pulmonary venography, cryoablation commenced and continued for 180 s, during which individual PVs were isolated. If LA–PV conduction persisted after cryoballoon ablation, an additional touch-up ablation was performed using an open-irrigated Thermo cool Smart Touch (Biosense Webster) or Flex Ability (St. Jude Medical) linear ablation catheter with a 3.5-mm tip.

In radiofrequency catheter ablation, circumferential ablation around both ipsilateral PVs was performed using an open-irrigated Thermo cool Smart Touch (Biosense Webster) or Flex Ability (St. Jude Medical) linear ablation catheter via an Agilis or Swartz Braided SL0 Transseptal Guiding Introducer Sheath (St. Jude Medical). Radiofrequency energy was applied for 30 s at each site using a maximum temperature of 42°C, maximum power of 35 W, and flow rate of 17 mL/min. PV isolation was considered complete when the 20-pole circular catheter no longer recorded any PV potentials.

We allowed additional ablation procedures in this study at the discretion of the operator, such as focal ablation for reproducible non-PV triggers; ablation of linear lesions, complex fractionated atrial electrograms (CFAE), and LVA homogenization; superior vena cava (SVC) isolation; and cavotricuspid isthmus linear ablation if patients had clinical or induced typical atrial flutter.

The endpoint of the linear ablation was a complete, bidirectional block across the linear lesion. This bidirectional conduction block was rechecked at the end of the procedure or > 20 minutes after the initial success of the conduction block. For the CFAE ablation, CFAE mapping was required during AF. The CFAE sites were identified by validated and automated algorithms of a 3-dimensional mapping system. The endpoint of the CFAE ablation was the elimination of all local CFAE sites or AF termination. AF termination was defined as a direct transition to sinus rhythm or to an organized atrial tachycardia or flutter. LVAs were homogeneously ablated using the open-irrigated radiofrequency catheter with the power set at 30W. The ablation catheter was moved in a point-by-point fashion. The endpoint of each radiofrequency application was an electrogram voltage reduction of > 50%. Isolation of the posterior LVA by PVI, roof, and bottom lines (box isolation) to avoid esophageal injury was permitted. In such cases, both entrance and exit blocks between the posterior wall and other left atrium were confirmed.

Voltage mapping

Following PV isolation, detailed voltage mapping was performed using a bipolar 3.5-mm tip catheter or multi-electrode mapping catheter during sinus rhythm or with pacing from the right atrium. In patients with persisting atrial fibrillation after PVI, voltage mapping was performed after electrical cardioversion. Voltage mapping was not completed due to unstable cardiac rhythm in 8of the total patients. (Figure 1)Mapping points were acquired to fill all color gaps on the voltage map using the electroanatomical mapping system. Respective fill and color interpolation thresholds were 15 mm and 23 mm using Carto 3 (Biosense Webster) and 20 mm and 7 mm using Ensite NavX (St. Jude Medical). Using Rhythmia (Boston Scientific), interpolation threshold was 5 mm.

Sites at which LVAs were recorded were then evaluated by high-density mapping to precisely delineate their extent, using the confidence module with the Carto 3 system and Ensite Automap with

Table 1: Patient characteristics.

	Group A (0-5 cm²) n=374	Group B (5-20 cm²) n=96	Group C (>20 cm²) n=40	P value A vs. B and C	P value B vs. C
Age, years	65±10	72±8	71±8	<0.001	0.479
Female, n (%)	67 (18)	47 (49)	21 (53)	<0.001	0.707
Body mass index, kg/m²	24.7±3.8	24.1±4.6	22.4±3.4	0.009	0.039
AF duration, months	4 (2, 11)	6 (3, 11)	4 (2, 17)	0.709	0.978
Hypertension, n (%)	207 (56)	47 (49)	24 (60)	0.494	0.240
Diabetes mellitus, n (%)	57 (15)	24 (25)	10 (25)	0.011	1.000
Heart failure, n (%)	92 (25)	31 (32)	10 (25)	0.207	0.398
CHA_2DS_2-VASc score	2.2±1.4	3.1±1.3	3.4±1.7	<0.001	0.301
BNP ≥ 100 pg/ml or NT-proBNP ≥ 400 pg/ml, n (%)	297 (79)	88 (92)	36 (90)	0.001	0.562
eGFR, ml/min	63±17	55±17	55±22	<0.001	0.887
Echocardiographic parameters					
Left atrial diameter, mm	43±6	43±6	47±7	0.006	0.010
Ejection fraction, %	58±13	57±13	60±14	0.734	9.448
Left ventricular mass, g	194±57	184±66	194±69	0.254	0.278
E/e'	10.4±3.8	12.4±6.5	12.4±5.6	0.001	0.985

Abbreviations: NT-proBNP, N-terminal pro-brain natriuretic peptide; eGFR, estimated glomerular filtration rate; E, diastolic early transmitral flow velocity; e', diastolic early mitral annular velocity

Table 2: Procedural background.

	Group A (0-5 cm²) n=374	Group B (5-20 cm²) n=96	Group C(>20 cm²) n=40	P value A vs. B and C	P value B vs. C
Number of procedures	1.4±0.3	1.4±0.6	1.6±0.3	0.304	0.116
Initial procedure	n=374	n=96	n=40		
PVI, n (%)	374 (100)	96 (100)	40 (100)	1.000	1.000
Mitral isthmus, n (%)	31 (8)	12 (13)	3 (8)	0.339	0.396
BOX isolation, n (%)	4 (1)	2 (2)	3 (8)	0.048	0.126
Roof line, n (%)	34 (10)	11 (11)	3 (8)	0.361	0.823
CFAE, n (%)	20 (5)	0 (0)	2 (5)	0.155	0.027
LVA ablation, n (%)	12 (3)	31 (32)	10 (25)	<0.001	0.398
Non PV foci, n (%)	2 (1)	1 (1)	2 (5)	0.090	0.152
SVC isolation, n (%)	2 (1)	0 (0)	1 (3)	0.793	0.120
CTI, n (%)	65 (17)	13 (14)	10 (25)	0.255	0.120
Additional procedure	n=102	n=35	n=23		
Redo PVI, n (%)	66 (65)	25 (71)	7 (30)	0.234	0.002
Mitral isthmus, n (%)	8 (8)	6 (17)	3 (13)	0.048	0.920
BOX isolation, n (%)	5 (5)	2 (6)	5 (22)	0.756	0.011
Roof line, n (%)	10 (10)	5 (14)	3 (13)	0.195	0.546
CFAE, n (%)	7 (7)	1 (3)	1 (4)	0.142	0.761
LVA ablation, n (%)	15 (15)	25 (71)	20 (87)	<0.001	0.035
Non PV foci, n (%)	31 (30)	15 (43)	8 (35)	0.215	0.689
SVC isolation, n (%)	27 (26)	1 (3)	1 (4)	0.002	0.326
CTI, n (%)	39 (38)	8 (23)	7 (30)	0.351	0.176

Abbreviations: PV, pulmonary vein; PVI, pulmonary vein isolation; CFAE, complex fractionated atrial electrogram; LVA, low voltage area; SVC, superior vena cava; CTI, cavo tricuspid isthmus

EnsiteNavX. Adequate endocardial contact was confirmed by distance to the geometry surface and stable electrograms. Each acquired point was classified according to the peak-to-peak electrogram as follows: >0.5 mV, healthy; and <0.5 mV, LVAs, with the band pass filter set at 30 to 500 Hz. The target number of mapping points was ≥100 with the 3.5-mm tip catheter and ≥1000 with the multi-electrode mapping catheter throughout the left atrium. Patients were categorized by LVA size into 3 groups. Patients in Group A had none or small LVAs less than 5cm^2; those in Group B had mildly or moderately diseased LA which contained LVAs less than 20 cm^2; and those in Group C had severely diseased LA which contained LVAs of more than 20 cm^2 (Figure 2).

Patient follow-up

If their clinical status was stable, patients were discharged two days after ablation. After a 3-month blanking period, they attended outpatient clinic visits and underwent 12-lead ECG monitoring at 1, 3, 6 and 12 months, and 24 h-Holter ECG monitoring every 6 months. Additional Holter monitoring was performed if arrhythmic symptoms occurred.

Repeat ablation was allowed for patients with recurrence of AF but was avoided during the blanking period. Repeat ablation during this period was counted as a recurrence just after the blanking period. Use of anti-arrhythmic drugs during the blanking period was allowed, but discontinuation after the blanking period was strongly recommended.

Study endpoints

The primary endpoint was AF-free survival after the last procedure without antiarrhythmic drugs. Either of two events was considered an AF/AT recurrence: (1) atrial tachyarrhythmia recorded on routine or symptom-triggered ECG during an outpatient visit, or (2) at least 30 s of atrial tachyarrhythmia during ambulatory ECG monitoring.

Statistics

Categorical variables are expressed as counts (percentages) and compared with the chi-squared test or Fisher's exact test. Continuous variables are expressed as mean (standard deviation) or median [interquartile range] and compared using Student's t-test and Mann–Whitney U test, respectively. Event-free survival rates were estimated by the Kaplan–Meier method. Univariate and multivariate logistic regression analyses were used to determine clinical factors associated with AF recurrence after the final procedure and extent of LVAs, wherein variables with a P value < 0.05 in the univariate models were included in the multivariate analysis. All analyses were performed using SPSS 26.0 (IBM Corporation, Armonk, NY). P values of less than 0.05 were considered statistically significant.

Results

Study subjects

This study enrolled 518 patients. After excluding 8 patient whose voltage mapping was not completed due to unstable cardiac rhythm, a total of 510 patients were stratified according to LVA area into 3 groups. 374 patients had no LVA (group A). The remaining 136 patients had LVAs after PVI and were allocated to groups B (n=96) and C (n=40) according to the size of their LVAs (Figure 1). Patient characteristics are shown in Table 1.Patients in group B and C were older than those in groups A, more female, had lower BMI, more diabetes, higher CHA_2DS_2VASc scores, higher BNP or NT-BNP levels, lower eGFR, larger left atrial diameter (LAD), and higher E/e'. On comparison of groups B and C, patients in group C had a significantly lower BMI and a larger LAD.

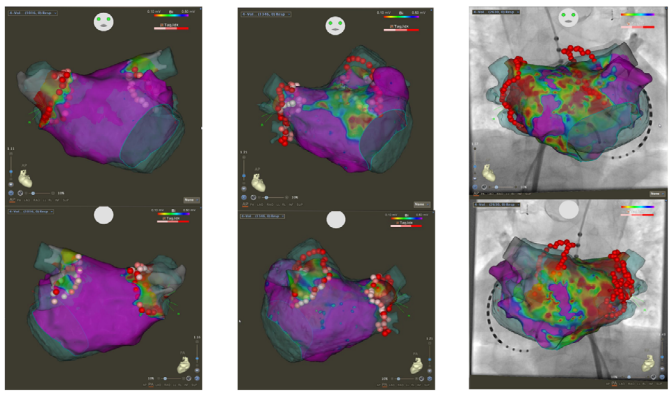

Figure 2: Example of LVA ablation in addition to PVI

Patients were categorized by LVA size into 3 groups. Patients in group A had no or small LVAs of less than 5cm2. Patients in group B had mildly or moderately diseased LA which contained LVA of less than 20 cm2. Patients in group C had severely diseased LA which contained LVAsof more than 20 cm2.

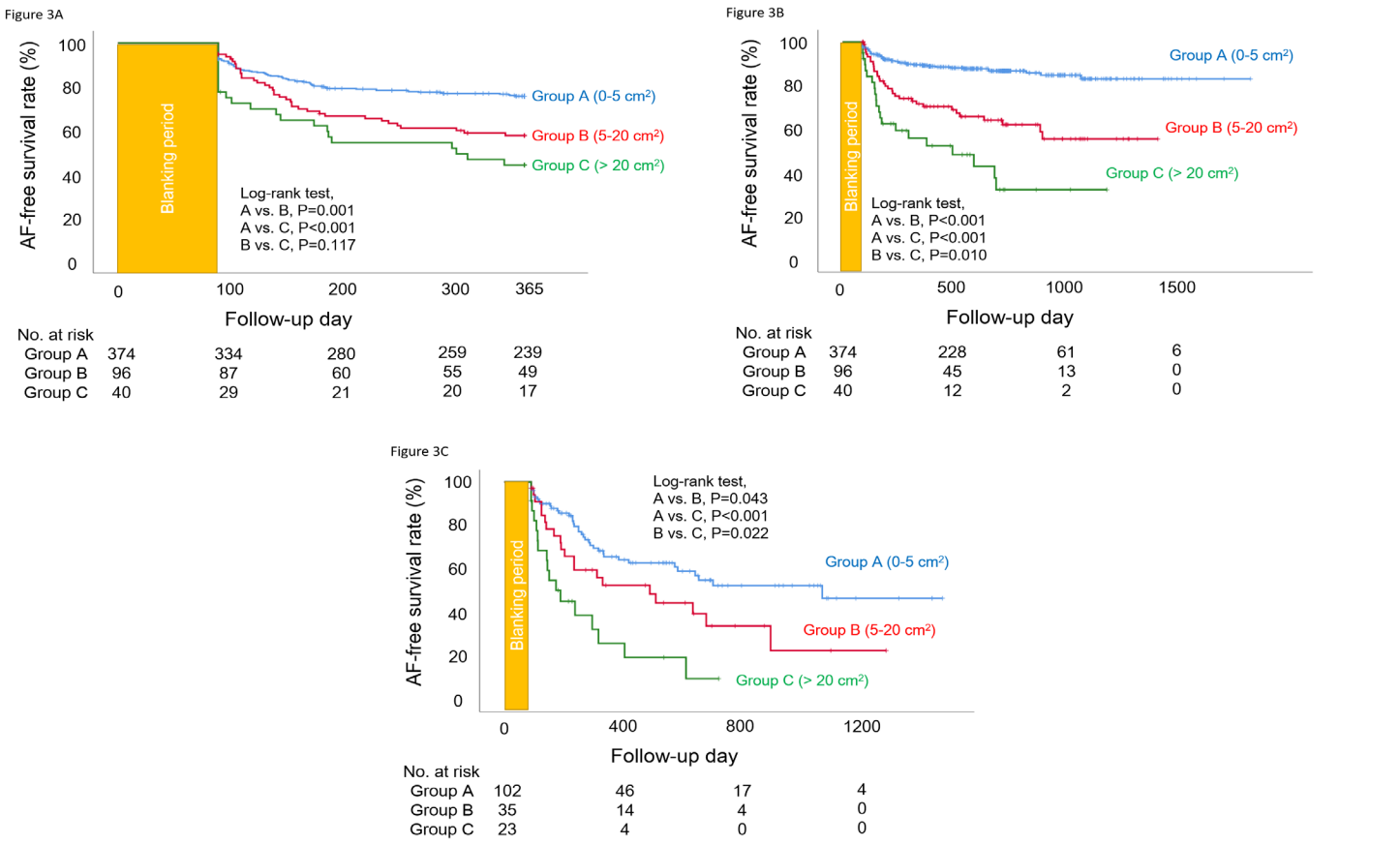

Figure 3: **AF recurrence-free survival rates.**

Kaplan-Meier curves for AF-recurrence-free survival are shown. Figure3A shows the analysis of AF recurrence at 1 year after the first ablation. Figure 3B indicates that clinical outcomes after multiple procedures depended on the extent of LVAs. Figure 3C shows the results of the post-re intervention analysis by extracting the re intervention group only.
Blue line, patients in group A); red line, patients allocated to group B; green line, patients allocated to group C. In Figures 3B and 3C, patients in group A demonstrated excellent rhythm outcomes. In contrast, those with extensive LVAs (group C) had a significantly lower AF-recurrence-free survival rate.

Ablation procedure

PVI was successfully completed in all patients, using Carto 3 in 479 (94%), Rhythmia in 20 (4%) and Ensite NavX in 11 (2%). The majority of cases underwent radiofrequency catheter ablation. Cryoballoon ablation was performed in 23 cases (5%).

Details of the initial and additional procedures are listed in Table 2. In the initial procedure, BOX isolation and LVA ablation were more frequently performed in group B and C. At the additional catheter ablation procedures, a higher percentage of PVI was completed in group

Table 3: **Factors associated with AF recurrence after the final procedure**

	Recurrence		Univariate			Multivariate		
	With n = 101	Without n =409	HR	95% CI	P value	HR	95% CI	P value
Age, years	68±9	67±10	1.02	0.999-1.05	0.055			
Female, n (%)	26 (26)	109 (27)	1.38	0.86-2.22	0.186			
Body mass index	24.6±5.0	24.4±3.8	0.99	0.94-1.05	0.825			
AF period, months	5 (2, 37)	4 (2, 10)	1.007	1.001-1.01	0.026	1.01	1.001-1.014	0.024
Heart failure, n (%)	19 (19)	114 (28)	0.92	0.56-1.52	0.917			
CHA_2DS_2-VASc score	2.6±1.6	2.4±1.5	1.15	0.998-1.33	0.054			
Estimated GFR, pg/ml	59±17	61±18	0.99	0.98-1.006	0.993			
Left atrial diameter, mm	44.5±6.7	42.8±6.1	1.04	1.01-1.08	0.027	1.02	0.978-1.068	0.324
Ejection fraction, %	58.0±14.4	58.0±12.5	1.001	0.98-1.02	0.872			
LVAs > 20 cm^2, n (%)	16 (16)	24 (6)	5.39	2.77-10.48	<0.001	8.82	3.32-23.45	<0.001

Factors with p <0.05 in the univariate analysis were incorporated in the multivariate analysis. HR, hazard ratio; CI, confidence interval, AF, atrial fibrillation; GFR, glomerular filtration rate; LVA, low-voltage area.

Table 4: Factors associated with extensive LVAs (>20cm²)

	Extensive LVAs (> 20cm²)		Univariate			Multivariate		
	With (n = 40)	Without (n = 470)	HR	95% CI	P value	HR	95% CI	P value
Age, years	71±8	67±10	1.06	1.02-1.10	0.004	1.04	0.97-1.12	0.275
Female, n (%)	21 (53)	114 (24)	3.45	1.79-6.65	<0.001	3.86	1.40-10.64	0.009
Body mass index	22.4±3.4	24.6±4.0	0.84	0.76-0.93	0.001	0.82	0.70-0.95	0.010
AF period, months	4 (2,17)	4 (2,11)	1.007	1.001-1.01	0.026	1.004	0.99-1.02	0.498
Heart failure, n (%)	10 (25)	122 (26)	0.94	0.45-1.98	0.871			
CHA_2DS_2-VASc score	3.4±1.7	2.3±1.4	1.59	1.28-1.97	<0.001			
Estimated GFR, pg/ml	55.2±21.8	61.2±17.0	0.98	0.97-0.999	0.037	0.99	0.96-1.01	0.355
BNP ≥ 100 pg/ml or NT-proBNP ≥ 400 pg/ml, n (%)	36 (90)	385 (82)	1.85	0.64-5.35	0.257			
Left atrial diameter, mm	47±6	43±6	1.10	1.04-1.15	<0.001	1.09	1.01-1.18	0.020
Ejection fraction, %	60±14	58±13	1.01	0.99-1.04	0.383			
E/e'	11.6±4.7	10.8±4.6	1.06	0.996-1.13	0.065			

Factors with p <0.05 in the univariate analysis were incorporated in the multivariate analysis.
HR, hazard ratio; CI, confidence interval, AF, atrial fibrillation; GFR, glomerular filtration rate; LVA, low-voltage area
BNP, Brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide

C and there was more LVA ablation in groupsB and C. In group A, SVC isolation was performed more frequently. There was no difference in the number of times ABL was performed among the three groups.

Ablation outcomes

AF recurrence was observed in 101 (20%) patients after 1.4±0.6 ablation procedures (maximum 4). Group A had 1.4±0.7 times, group B had 1.4±0.6 times, and group C had 1.6±0.6 times, with no significant difference between the groups (P=0.20). On analysis of AF recurrence at 1 year after the first ablation (Figure 3A), group Aperformed significantly better than the other groups, but there was no difference between groups B and C. Comparison of clinical outcomes after multiple procedures in the three groups showed that the results depended on the extent of LVA (Figure 3B). Namely, the group without LVA (group A) had an extremely high success rate despite persistent AF. In contrast, more than half of the patients with extensive LVAs (group C) developed recurrence within a few years, even after multiple treatments. The poor prognosis of patients with extensive LVAs was also seen in the analysis of patients who were retreated (Figure 3C).

Multivariate analysis of AF-free survival after the last procedure showed thatLVAs> 20cm² and longer AF duration were independent factors associated with AF recurrence (Table 3).

The percentage of patients taking anti arrhythmic medication at the last follow-up was 9% in group A, 17% in group B, and 10% in group C, with no significant difference between groups (P=0.12).

Predictors of extensive LVAs

Because the extent of LVA after initial PVI might contribute significantly to clinical outcomes, we performed additional analyses of factors that predict extensive LVAs. Univariate analysis revealed that advanced age, female, lower BMI, longer AF duration, higher CHA_2DS_2-VASC score, lower renal function, and large LAD were significant predictors for extensive LVAs(Table 4). After multivariate analysis, female, low BMI, and large LAD were considered to be independent factors associated with extensive LVAs(Table 4).

Discussion

In this study, we found that the extent of LVAs was an independent predictor for recurrence even after multiple procedures. The efficacy of catheter ablation was limited in patients with extensive LVAs. In patients with extensive LVAs, the indications and strategies for additional treatment should be carefully considered. In addition, female sex, lower BMI, and larger LAD were shown to be predictors of extensive LVAs. These findings suggest that the results of voltage mapping after initial PVI can help predict procedural success of subsequent catheter ablation.

Efficacy of AF ablation in patients with no or limited LVAs

In this study, group A patients without LVA had a good prognosis up to the late phase after multiple procedures. This result is consistent with previous studies of LVA-guided therapy[12-14]. Considering the implications of LVAs on AF development, LVAs reflect atrial fibrosis[15,16] and fibrotic remodeling tissue leads to slow conduction and short action potential duration, which facilitates reentry[17,18]. In group A patients who did not have these arrhythmic substrates, many non-PV procedures such as SVC isolation were performed at the time of additional procedures, suggesting that if the AF initiator could be treated, the results might be comparable to those of paroxysmal patients.

Efficacy of ablation in patients with LVAs

As described above, clinical outcomes were worse in patients with LVAs after initial PVI than in the group without LVA after multiple procedures, when patients with LVAs were compared with each other, a significant difference in clinical outcomes was seen after additional procedures, depending on the extent of the LVA.

Although PV reconnection is still considered a major cause of AF recurrence after initial ABL[19], this factor seems to have diminished in terms of post-retreatment outcomes. At repeat procedures, the operator used his or her own discretion to determine treatment strategy for non-pulmonary veins, and most of the ablation targeted the LVA. This result

suggests that LVA ablation, linear ablation, and CFAE can be effective adjunctive ablation with concomitant PVI. [4,5]

It has been reported that LVA is associated with fibrosis of the left atrium. Extensive LVAs were associated with more residual fibrosis.[20] Development and progression of atrial fibrosis, which plays an important role in AF maintenance, is the hallmark of structural remodeling in AF. The presence of extensive LVAs can lead to multiple or complex areas of arrhythmogenicity. Extensive LVAs could have increased the area that could not be treated by ablation therapy, which might have resulted in poor clinical outcomes.

On the other hand, it must also be considered that fibrosis may simply be the final step of a remodeling cascade which includesmyocyte architectural changes, ion channel dysfunction, connexin disarray and disruption of fiber orientation, all of which might precede scarring but not be seen on voltage mapping or imaging.[20] Based on this concept, the extent of an LVA might indicate the progression of fibrosis throughout the atrium. This might in turn suggest that patients with extensive LVAs are more likely to develop new arrhythmogenic features in the future.

The results of our study suggest that the benefit of beyond PVI therapy applies to patients with moderately advanced remodeling, such as those in group B. Table 2 and Figure 3 show that group C, with extensive LVAs, had a high recurrence rate even when PVI was complete. This suggests that clinical outcomes in patients with extensive LVA sarenot yet sufficient, even with additional treatment of PVIs with high durability. Ablation therapy can also create new iatrogenic LVAs, which may limit the effectiveness of treatment in cases that already have extensive LVAs. These cases may require concomitantuse of appropriate anti-arrhythmic drugs, in addition to ablation therapy.

Clinical factors associated with extensive LVAs

Although several methods for preoperative prediction of the presence of LVAs have been reported[21-23], the present study showed that widespread LVAs worsen the clinical prognosis. We identified the following as independent predictors of extensive LVAs: female, low BMI, and large LAD (Table 4). These factors have been reported to be related to LVAs in the past, and we discuss them here with reference to these reports.

These previous reports identified mechanisms underlying the sex differences in atrial fibrosis.[24] On histological analysis of atrial tissue, females showed stronger expression of CX40 than males, which indicates remodeling-induced change in connexins.[25] In addition, fibrosis-related genes were up regulated in post-menopausal woman with AF.[26] Clinically, females reportedly experience AF recurrence more frequently than males during long-term follow-up after AF ablation, likely due to non-PV arrhythmogenicity.[27]

The reason why low BMI and large LAD are associated with extensive LVAs may be that they both reflect wall stress on the LA. As reported previously, LVA is are sult of the progression of remodeling. LA remodeling in AF patients is suggested to be associated with continuous internally generated stretch and wall stress.[9,28-30]Anatomical contact with external structures surrounding the LA provokes the perpetuation of AF by arrhythmogenic substrates in patients with persistent AF.[31,32] In patients with low BMI, the distance between the LA and external structures such as the vertebral bodies may be close enough to trigger the development of LVA.

Clinical implications

It has become widely known that LVA predicts the outcome of the first treatment.[10,12,21,33] Our present results indicate that evaluating the extent of LVA can predict the clinical course of the second and subsequent treatments.

Limitations

Several limitations of our study warrant mention. The main limitation is the study's retrospective design, which meant that procedures were not standardized but rather at the discretion of the operator. Although prospective studies are necessary to solve these problems, standardization of procedures and long-term observation in an era of constantly improving strategies is not easy. Second, our follow up did not include routine continuous monitoring with implanted devices or transtelephonic electrocardiographic monitoring, and our AF-recurrence-free rate might therefore be underestimated. Third, since we performed voltage mapping using either bipolar 3.5-mm tip catheters or multi-electrode mapping catheters, the distribution of LVAs might have changed, given that multielectrode catheters produce smaller LVA measurements than ablation catheters.[34] Fourth, our conduct of voltage mapping after the completion of PV isolation and in the left atrium only might have influenced the prevalence of LVAs. Fifth, patients with the worst prognosis, namely those in whom a voltage map could not be obtained after the first PVI, were excluded. Sixth, the cut-off values (5 cm^2 and 20 c^2) used for grouping were arbitrary. Finally, statistical analyses were limited by the relatively small size of the study population.

Conclusion

Extensive LVA after initial PVI was associated with no significant clinical benefit despite multiple catheter ablation procedures. Predictors of extensive LVAs included female sex, lower BMI and large LAD.

Acknowledgments

Ethical approval: This study complied with the Declaration of Helsinki. The protocol was approved by our institutional review board.

Informed consent: Written informed consent for ablation and the use of data in this study was obtained from all patients.

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Does Duration of Symptoms Reliably Predict Detection of Left Atrial Thrombus in Newly Diagnosed Atrial Fibrillation

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Abstract

Background: Large prospective trials attribute minimal thromboembolic risk for cardioversion of atrial fibrillation (AF) when duration of symptoms is shorter than 48 hours. Our goal is to compare the prevalence of left atrial appendage (LAA) thrombus as demonstrated by a Trans esophageal echocardiography (TEE) exam between patients presenting with less or more than 48 hours of AF symptoms.

Method: Observational cohort study including consecutive patients hospitalized with primary diagnosis of new onset AF, not previously treated with oral anticoagulation. All patients underwent TEE to exclude LAA thrombus, regardless of symptoms duration. Patients were divided into two groups based on AF duration: 1) early presenters: up to 48 hours, 2) later presenters: longer than 48 hours.

Results: The study included 122 patients mean age 65.8 years). The "early presenters" were younger, with less co-morbidities. LAA thrombus was detected in 13(21%) of 62 early presenters, compared to 20 (33%) of 60 patients of the second group (P=0.12). Significant predictors of LAA thrombus in the whole cohort by univariate analysis were ≥65 years of age (1.051, P=0.017), acute heart failure (2.394, P=0.038), and history of coronary artery/ peripheral vascular disease (2.7, P= 0.019). Notably neither duration of symptoms nor CHA2DS2-VASc score significantly predicted LAA thrombus. Inmultivariate analysis, only age ≥65 was found to be a significant predictor of LAA thrombus.

Conclusion: LAA thrombus in patients presenting within 48 hours of AF symptoms onset is not uncommon. Duration of symptoms is not reliable for excluding LAA thrombus.

Introduction

There is strong evidence confirming the relation between left atrial appendage (LAA) thrombus and cardioembolic events. Atrial fibrillation (AF) autopsy studies showed high frequency of LAA thrombus and embolism in deceased AF patients [1-3]. Early transoesophageal echocardiography (TEE) studies demonstrated a much higher prevalence of LAA thrombus in newly diagnosed AF patients in the setting of cerebro-vascular accident (CVA) or transient ischemic attack (TIA) [4]. Prospective studies following AF patients with confirmed LAA thrombus showed increased risk for thromboembolic events [5]. Cardioversion when not preceded by adequate anticoagulation therapy is associated with increased risk for stroke [6-8], however, exclusion of LAA thrombus minimizes this risk [9-10].

Patients presenting with new onset AF have increased risk for thromboembolic events [11]. Conventionally, patients presenting within 48 hours of symptoms onset deemed to be in lower risk and cardioversion may be attempted [12,13]. However, cardioversion is not risk-free, as 6.4% of strokes related to AF occur after cardioversion [14]. Demonstration of LAA thrombus by TEE, usually performed prior to cardioversion in patients presenting beyond 48 hour of symptoms onset, is associated with significant risk of thromboembolic events and prohibits cardioversion [15].

Earlier studies showed that LAA thrombus in acute AF (less than 48hours of duration) is not uncommon and thromboembolism among uncoagulated patients undergoing cardioversion is not negligible, especially when presenting later than 12 hours of symptoms onset in patients with risk factors [7,16,17]. International Guidelines recommendations are permissive for cardioversion in patients presenting early (symptoms less than 48 hours), when anticoagulation is started before cardioversion [12,13]. However, the short time between anticoagulation and cardioversion might not be enough for thrombus resolution, supposed LAA thrombus is present, and these patients' risk for thromboembolism might be significantly high.

Key Words

Atrial Fibrillation, Duration, Thrombus.

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Table 1: Baseline characteristics

		Duration of AF symptoms before presentation		
	All (n= 122)	≤48 Hours (n= 62)	>48 Hours (n= 60)	p value
Sex (female) n. (%)	68 (55.7)	32 (51.6)	36 (60)	0.35
Age (mean) (years)	65.8	63.1	68.8	0.003
Hypertension n. (%)	86 (70.5)	38 (61.3)	48 (80)	0.023
Diabetes mellitus n. (%)	47 (38.5)	18 (29)	29 (48.3)	0.028
History of heart failure n. (%)	28 (23)	11 (17.7)	17 (28.3)	0.164
Acute heart failure n. (%)	33 (27)	6 (10)	27 (45)	0.00001
History of stroke/TIA n. (%)	11 (9)	5 (8)	6 (10)	0.27
History of CAD/PVD n. (%)	32 (26.2)	15 (24.2)	17 (28.3)	0.6
CKD (eGFR≤ 60 ml/min) n. (%)	14 (11.5)	4 (6.5)	10 (16.6)	0.08
Smokers n. (%)	20 (16.4)	9 (14.5)	11 (18.3)	0.57
Hyperlipidemia n. (%)	78 (63.9)	36 (58)	42 (70)	0.17
CHA2DS2-VASc (mean)	3.2	2.60	3.8	0.0003
CHA2DS2-VASc >1 in men or >2 in women	88 (72)	37 (60)	51 (85)	0.002

TIA: transient ischemic attack, CAD: coronary artery disease, PVD: peripheral vascular disease, CKD: chronic kidney disease

This study aims to evaluate the presence of LAA thrombus in all AF patients who were admitted to our department and were candidate for cardioversion regardless of symptoms duration, and to characterize early presenting patients with LAA thrombus, for whom cardioversion might be risky.

Methods

All patients who were admitted to the cardiology department in Poriya Medical Centre, in the north of Israel, between 01.2016 and 01.2019, hospitalized for newly diagnosed AF and not treated with anticoagulation and were candidates for cardioversion, underwent a TEE study to exclude LAA thrombus, regardless of AF symptoms duration, as defined by local policy, contrast was not routinely injected. We retrospectively queried our local hospital digital data base for patient's medical background and TEE reports. Symptom's duration was determined by reviewing emergency room records and admission records. Patients whom symptoms duration were undetermined (e.g., asymptomatic patients), or unmentioned in the medical records were excluded. Patients were divided to 2 groups: patients with symptoms ≤48 hours (early presenters) and patients with symptoms > 48 hours (late presenters). In addition, digital medical records were followed up retrospectively for 12 months after admission, all cerebrovascular accidents, transient ischemic attacks, or peripheral arterial emboli, as determined by using clinical and imaging data (at discretion of neurologists or vascular surgeons)were included.

Statistical analysis

Data were analyzed with SPSS software, Version 18.0 (SPSS Inc.; Chicago, IL, USA). Categorical variables were expressed as percentages and continuous variables as means ± standard deviations. Chi-Square was applied for categorical variables, and Independent T test for continuous variables as appropriate to assess the differences between patients with AF duration of ≤48 hours versus those with >48 hours before presentation to the hospital. Statistical significance was defined by a $p < 0.05$.

A univariate logistic regression model was used to predict the presence of LAA thrombus. A multivariate logistic regression was performed, using the backwards model. All covariates whose univariate statistical significance was < 0.05 were forced into a multivariate model. Backwards variable elimination was then used to develop a parsimonious regression model. These variables include in the multivariate logistic regression were age ≥65, history of coronary artery disease (CAD) or peripheral vascular disease (PVD), and acute heart failure. Those variables whose adjusted statistical significance was < 0.1 were retained in the final model. Odds Ratio (OR) with a 95% CI and p-values were derived from the Wald chi-square test.

We assessed the differences in the rate of systemic emboli (CVA/TIA) during the first year of follow-up between patients with and patients without LAA thrombus. Statistical significance considered to be two-sided p-values of <0.05.

Results

After querying our echo database for AF and TEE for LAA thrombus exclusion before cardioversion between 01/2016 and 01/2019, 136 patients were located. Reviewing of emergency room and admission records revealed that among them 62 patients presented up to 48 hours of symptoms, and 60 patients with symptoms lasting longer than 48 hours. In 14 patients, symptoms duration could not be ascertained, either due to lack of proper recording, or patients were not aware of any symptoms; this group was excluded from the final analysis. Mean age of the cohort was 65.8 years. Patients presenting beyond 48 hours of symptoms were older (68.8 vs. 63.1 years, p=0.003), had significantly more comorbidities, including hypertension (80% vs 61.3%, P=0.023) and diabetes mellitus (48.3% vs. 29%, p=0.028). Chronic kidney disease (CKD) was more common in patients presenting lately but the difference did not reach statistical significance(16.6% vs. 6.5%, respectively, P=0.08). Notably, sex, hyperlipidemia, coronary CAD)/PVD, heart failure, history of CVA/TIA, and smoking status were not significantly different among the two groups as described in table 1. Acute heart failure was more common among late presenters (45%) compared to early presenters (10%, p=0.00001). Mean CHA_2DS_2-VASc [Congestive heart failure, hypertension, Age ≥75 years, diabetes mellitus, stroke, vascular disease, Age 65-74, sex category (female)] score was 3.2. Later presenters had significantly higher CHA_2DS_2-

Table 2: Logistic regression model for predicting left atrial appendage thrombus

	Odd ratio	95% CI	p value
Symptom's duration > 48 hours	1.063	0.598-1.890	0.835
Age ≥ 65 years	1.051	1.009-1.095	0.017
CHA2DS2-VASc >1 in men or >2 in women	1.18	0.958-1.454	0.119
Sex (male)	0.689	0.317-1.499	0.348
Acute heart failure	2.394	1.049-5.462	0.038
Hypertension	1.692	0.667-4.295	0.268
History of Heart failure	2	0.856-4.673	0.109
History of stroke/TIA	0.818	0.212-3.158	0.771
Diabetes Mellitus	0.61	0.271-1.382	0.237
History of CAD/PVD	2.7	1.18-6.26	0.019

Table 3: multivariate logistic regression model for predicting left atrial appendage thrombus

	Odd ratio	95% CI	p value
Age ≥65	1.05	1.000-1.089	≤0.05
Acute heart failure	1.76	0.738-4.216	0.20
History of CAD/PVD	2.197	0.928-5.199	0.07

VASc scores compared to early presenters, however mean scores of both groups, separately, were high (3.8 vs. 2.6, respectively, P=0.003). CHA_2DS_2-VASc >1 in men or >2 in women was more common among patients presenting beyond 48 hours (85%) compared to ≤48 hours (60%, p=0.002).

LAA thrombus was detected in 13(21%) of 62 early presenters, compared to 20 (33%) of 60 patients with longer than 48 hours symptoms duration (P=0.12). Average CHA_2DS_2-VASc score in early presenters who had LAA thrombus was 3.2, compared to 2.4 in early presenters without LAA thrombus (p=0.06). Three (12.5%) of 24 patients who had CHA_2DS_2-VASc score of 0 or 1 had LAA thrombus. Univariate logistic regression analysis for predicting LAA thrombus in the whole cohort found the following variables significantly related to LAA thrombus detection: Age ≥65 (OR=1.051, P=0.017), acute heart failure (OR= 2.394, P=0.038), and history of CAD/PVD (OR= 2.7, P=0.019).

Neither symptoms duration, CHA_2DS_2-VASc, sex, hypertension, history of heart failure, history of CVA/TIA, nor diabetes mellitus, were found to be significant predictors of LAA thrombus, as described in table 2. In multivariate analysis including age ≥65, history of CAD/PVD, and acute heart failure at presentation, only age ≥65 was found to be a significant predictor of LAA thrombus (OR= 1.05, P≤0.05) (table 3).

Detection of LAA thrombus was significantly related to a cardioembolic event in the first year (OR= 14.4, P=0.001), but not in the first month of follow up (OR=2.8, P=0.26) (table 4).

Discussion

The main result we found is the surprisingly high prevalence of LAA thrombus among AF patients, presenting within 48 hours of symptom onset, compared to previously reported data. In our study, 21% of AF patients, presenting within 48 hours of symptoms onset, had LAA thrombus. Interestingly, this rate is not statistically different compared to AF patients presenting beyond 48 hours (33%, p=0.12) despitesignificantly higher mean CHA_2DS_2-VASc score among the latter group. Age ≥65, history of CAD/PVD, and acute heart failure were found to be significant predictors of LAA thrombus in univariate analysis, among which only age ≥ 65 stayed significant after multi variate analysis, even though there was a trend to significance regarding CAD/PVD.

In one study comparing thromboembolic events in short term AF, 4% of AF patients, not pre-treated with anticoagulation, had LAA thrombus [7]. Reduced left ventricular function and increased left atrial volume were significantly associated with increased risk for LAA thrombus [7]. In a study evaluating the clinical outcome of stroke/TIA at 30 days after cardioversion in acute AF patients, thromboembolic events were rare (0.2%) [8]. However, risk increased significantly (9.8%) when adjusted for heart failure and diabetes [8]. In another study, 14% of 63 patients presenting within 72h of symptom onset had LAA thrombus, that was the highest prevalence reported thus far [16].

In univariate logistic regression, age ≥65, acute heart failure, and history of CAD/PVD were related to LAA thrombus detection. Patients presenting with acute heart failure are usually older, with more co morbidities including CAD/PVD. Heart remodeling, structural and valvular abnormalities are more common among these patients, being a substrate for LAA thrombus formation and increasing risk for thromboembolism. This subgroup should be treated with extra vigilance, as on one hand, urgent cardioversion might be indicated if tachyarrhythmia is thought to be major contributor to deteriorating hemodynamics, overweighing the risk of thromboembolism. On the other hand, when mechanisms other than AF prevail, thorough considerations should be made before cardioversion as increased risk for LAA thrombus and hence thromboembolic event exists, regardless of symptoms duration. We believe every effort should be done to postpone cardioversion until proven safe either by ruling out LAA thrombus or allowing sufficient time for anticoagulation, except in cases when hemodynamic instability is present.

Interestingly, CHA_2DS_2-VASc >1 (>1 in men or >2 in women) was not found to be a significant predictor of LAA thrombus. This does not mean that CHA_2DS_2-VASc > 1 is not a risk factor for thromboembolic events, but it shouldn't be used to predict LAA thrombus in these group of patients. Mean CHA_2DS_2-VASc score was high in both groups(2.8% Vs. 3.8%, P=0.0003). High CHA_2DS_2-VASc score (>2 for males, and >3 for females) among early presenters in our cohort may blurred the real impact of CHA_2DS_2-VASc score upon LAA thrombosis. Furthermore, our cohort included only patients who were hospitalized for AF that was not resolved spontaneously in the emergency department, or within several hours of admission. In our experience, most of the patients with acute AF, that resolved spontaneously, are younger and have less comorbidities, and therefore likely have less risk for LAA thrombus.

AF duration was not a significant predictor of LAA thrombus detection. This finding should be kept in mind when addressing patients presenting acutely within 48 hours of symptoms, as in contrary to general practice which refer low thromboembolic risk for cardioversion of short duration AF. Indeed, according to the recently published 2020 ESC guidelines, it may be ideal to perform elective cardioversion after 3 weeks of anticoagulation or after TEE excluding LAA thrombus in patients with AF duration 12-48 hours and CHA_2DS_2-VASc ≥2 in males and ≥ 3 in females even it is a IIa indication according to this guideline for early cardioversion without TEE in patients with an AF duration of < 48 hours [18]. Furthermore, a wait-and-watch approach with rate control medication only and cardioversion when needed within 48 h of symptom onset should be considered as it was found to be as

Table 4: Pearson chi square testing LAA thrombus as predictor for cardioembolic events

	OR	p value
1 month follow up	2.796	0.265
1 year follow up	14.419	0.001

safe as and non-inferior to immediate cardioversion of recent-onset AF, which often resolves spontaneously within 24 h [19].

An association between LAA thrombus and a thromboembolic event (TIA, stroke, systemic embolism) at first year after admission was demonstrated. Interestingly, such an association was not found for events in the first month. LAA thrombus may perform as a general predictor of thromboembolic risk, rather than just a harbinger for a threatening event. A challenging scenario that may clarify this point is detecting LAA thrombus in low thromboembolic risk, as determined by a CHA_2DS_2-VASc score. We believe such patients should be treated chronically with anticoagulation.

Limitations

First, it is single center observational study. Second, the study is limited by the retrospective methodology and relatively small sample size. Univariate, and multivariate analysis for predictors of LAA thrombus should be cautiously interpreted. The small sample size, not powered to detect difference, may explain the reason that CHADS-VASc score was not associated with LAA thrombus, and age>65 had increased risk for LAA thrombosis by only 5%. Unfortunately, data regarding anticoagulation status for 1 month and 1 year after admission was not reliably found for all patients; if it was, this would have provided perspective as to why there is an increased risk of cardio embolic event in this population at one year. Although symptoms duration was determined after careful review of emergency room and admission records, the reporting was not homogenous, and symptoms were diverse, limiting the possibility to further subdivide early presenters into groups of 24 hours and 48 hours. Another drawback, most patients in the study didn't have transthoracic echo performed in hospital as local policy doesn't mandate it for AF patients planned for cardioversion. Data regarding actual atrial size is lacking and association of left atrial size and LAA thrombosis could not be assessed. Mean LAA velocity was not routinely assessed during TEE and relation between this variable and LAA thrombosis could not be assessed. Determination of thromboembolic events was based on clinical and imaging data at discretion of neurologists and vascular surgeons. Head MRI, head and neck MRA/CTA were not regularly performed, and some events could be an atherothrombotic complication rather than cardioembolic etiology. Finally, the study population was characterized by high CHA_2DS_2-VASc, which may contribute to the high prevalence of LAA thrombus and diminish generalizability.

Conclusion

LAA thrombus is not uncommon in patients not treated with anticoagulation presenting with acute AF, even when assumed for a short duration (less than 48 hours). Attempts to clarify LAA thrombus may be needed before cardioversion is performed in high-risk patients, mainly patients ≥65 years of age, presenting with acute heart failure, and history of CAD/PVD.

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Fluoroless Catheter Ablation of Atrial Fibrillation: Integration of Intracardiac Echocardiography and Cartosound Module

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Abstract

Objectives: To evaluate the feasibility, safety, and clinical efficacy of non-fluoroscopic radiofrequency catheter ablation of atrial fibrillation (AF) in comparison to traditional fluoroscopy-guided ablation in a local Canadian community cohort.

Methods: We retrospectively studied consecutive patients with paroxysmal and persistent AF undergoing pulmonary vein isolation (PVI) guided by intracardiac echocardiography (ICE) and Carto system (CartoSound module). ICE-guided PVI without fluoroscopy (Zero-fluoro group) was performed in 116 patients, and conventional fluoroscopy-guided PVI (Traditional group) was performed in 131 patients.

Results: Two hundred and forty-seven patients with AF (60.7% male; mean age: 62.2 ± 10.6 years; paroxysmal AF =63.1%) who underwent PVI were studied. Mean procedure times were similar between both groups (136.8±33.4 minutes in the zero-fluoro group vs. 144.3±44.9 minutes in the traditional group; p=0.2). Acute PVI was achieved in all patients. Survival from early AF recurrence was 85% and 81% in the zero-fluoro and traditional groups, respectively (p = 0.06). Survival from late AF recurrence (12-months) between the zero-fluoro and traditional groups was also similar (p=0.1). Moreover, there were no significant differences between complication rates, including hematoma (p = 0.2) and tamponade (p = 1),between both groups.

Conclusions: Zero-fluoroscopy ICE and CartoSound-guided AF ablation may be safe and feasible in patients undergoing PVI compared to conventional fluoroscopy-guided ablation.

Introduction

Radiofrequency ablation (RFA) of atrial fibrillation (AF) is performed under fluoroscopic guidance and, therefore, carries a risk of radiation for both the patients and the medical staff attending to the procedure[1–4]. Although three-dimensional (3D) mapping and newer imaging modalities have allowed for catheter visualization and successful ablation, there has been increasing interest to use minimal or zero fluoroscopy during AF ablation to limit radiation dose exposure [5–7]. Recently, fluoroless RFA procedures guided by intracardiac echocardiography (ICE) and 3D mapping were safely performed with high success for complex arrhythmias [8–12]. To better understand the applicability of these findings in a local Canadian population, the present analysis examined the feasibility, safety, and clinical efficacy of non-fluoroscopic RFA in comparison to traditional fluoroscopy-guided ablation in patients with AF.

Key Words

Atrial Fibrillation; Catheter Ablation; Intracardiac Echocardiography; Fluoroscopy; Three-Dimensional Mapping.

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Materials and methods

Study population and protocol

From October 2017 to November 2020, 247 consecutive patients undergoing RFA for symptomatic, drug-refractory paroxysmal AF (PAF) or persistent AF were retrospectively studied. To minimize inter operator bias, one operator (AP) conducted RFA. Our center has performed Fluoroless AF ablations as the standard of care and first option since 2019. Cases before and after the implementation of the Fluoroless AF program were compared. During Fluoroless ablations, the operator and other medical staff attending to the procedure did not wear lead aprons and the fluoroscopy system was inactivated and removed. The operator (A.P) has been practicing Fluoroless AF ablation for two years. The study was approved by the local Institutional Research Ethics Board.

Procedure duration, acute procedural success, complications, and recurrence rates were recorded. Procedure duration was recorded from

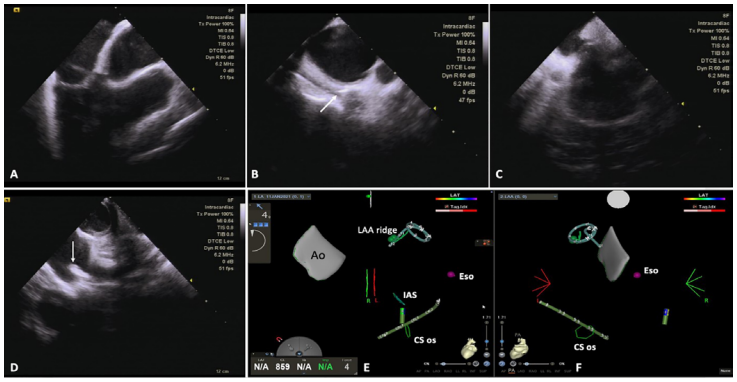

Figure 1: **Illustratrive description of fluoroless AF ablation (ICE+CartoSound).**

A:Main view showing aortic root, tricuspide valve, RV, and RVOT; B: Clockwise rotation of ICE catheter showing posterior aspect of left atrium along with esophagus and tip of esophagial probe (arrow); C: Interatrial septum; D: View of LAA ridge (arrow) between LAA and LSPV; E-F: Carto images of anatomical landmarks obtained by ICE. Left lateral and PA views showing aorta (Ao), interatrial septum (IAS), coronary sinus ostium (CS os), left atrial appendage ridge (LAA ridge), and tip of esophagial probe (Eso).

initial venous access until final sheath removal after the completion of the RFA procedure. Acute pro¬cedural success was determined by both entrance and exit blocks of the pulmonary veins. Recurrence was defined by the occurrence of arrhythmia after the blanking period (three months) following RFA.

Pre- and intra-procedural description

Transesophageal echocardiography was performed to rule out intracardiac thrombus in the left atria and the left atrial appendage. Antiarrhythmic drugs were discontinued for approximately five half-lives except for amiodarone, which was discontinued for >2 weeks before the RFA procedure. Patients were asked to hold oral anticoagulation 24 hours before the procedure and a bolus of heparin (100 U/kg) was administered intravenously before the transseptal puncture. Intravenous heparin was administered to target an activated clotting time above 300 seconds.

Under sterile draping in the usual fashion, three 9 French venous sheaths were placed in the right femoral groin. An 8-French Soundstar catheter (Biosense Webster, Irvine, CA) was inserted into the right atrium. After activation of the Carto Sound module, the following anatomical landmarks were marked in the mapping system: aorta, interatrial septum, coronary sinus ostium, and left atrial appendage ridge. An esophageal temperature probe was placed adjacent to the posterior wall of the left atrium and the level of the tip of the probe was marked on the mapping system with the help of ICE and CartoSound (Figure 1). A diagnostic catheter (IBI Inquiry, Abbott Medical) was placed into the coronary sinus under ICE, EGM, and CartoSound guidance. Transseptal access was obtained under ICE guidance as follows: the wire was advanced into the right atrium, and once identified, directed into the superior vena cava (SVC). A long SL-1 sheath and dilator (Abbott Medical) were advanced over the wire into the SVC. After the wire was removed, a transseptal puncture needle (Brocken brough, Abbott Medical) was advanced to within the dilator tip. The unit was pulled inferiorly and directed to a particular region of the interatrial septum. Once "tenting" was observed, a puncture was performed and confirmed with both ICE visualization and microbubble injection. Single transseptal access was obtained in all patients (Figure 2 and Supplementary Video). In case of failure to obtain proper tenting of the septum, we used an ablation catheter to direct the SL1 sheath to the septum, which was marked on the mapping system. The ablation catheter was then removed and replaced with a dilator and BRK needle. Transseptal puncture was performed afterward. Then, a circular Lasso catheter (Biosense Webster, Irvine, CA) was placed in the left atrium and detailed electro-anatomical mapping of the left atrium was performed with the CARTO 3 system (Biosense Webster, Irvine, CA). Following the completion of mapping, the Lasso catheter was exchanged with a contact-force (CF) sensing bidirectional Thermo cool Smart Touch catheter (Biosense Webster, Irvine, CA) to start the RFA procedure. Point-by-point wide antral circumferential ablation with RF was performed in all patients. RF energy was applied at 30 to 35 Watts in the anterior aspect of pulmonary veins; however, in the posterior aspect of the pulmonary veins, RF energy was applied at 20-25 Watts due to the close proximity to the esophagus. Targeted CF was 10-20 grams except in areas that were in close proximity to the esophagus where targeted CF was 5-10 grams. Ablation index was used (450 for the anterior wall, 350-400 for the posterior wall). If AF persisted after isolation, electrical cardioversion was performed to restore sinus rhythm. Additional lesion delivery was left at the operator's discretion and could have included LA roofline, LA posterior wall isolation, and mitral isthmus line. It is worth mentioning that CartoSound was used in order to guide the Fluoroless procedure, including annotation of adjacent tissues (esophagus, aorta, interatrial septum, LAA ridge),

Table 1: **Baseline characteristics of patients undergoing traditional and zero-fluoro ablation of atrial fibrillation.**

	Total (n = 247)	Zero-fluoro (n = 116)	Traditional (n = 131)	P-Value
Age (years)	62.2 (10.6)	61.9 (10.6)	62.6 (10.6)	0.5
Gender, male	150 (60.7%)	86 (65.6%)	64 (55.2%)	0.1
PAF	152 (63.1%)	78 (62.4%)	74 (63.8%)	0.9
Comorbidities				
Hypertension	129 (52.4%)	65 (50%)	64 (55.2%)	0.4
Diabetes	28 (11.4%)	14 (10.8%)	14 (12.1%)	0.9
Sleep Apnea	67 (27.2%)	34 (26.2%)	33 (28.4%)	0.7
Stroke	9 (3.7%)	3 (2.3%)	6 (5.2%)	0.3
CAD	38(15.4%)	16(12.3%)	22(19%)	0.2
Ischemic CM	16(6.5%)	5(3.8%)	11(9.5%)	0.1
HCM	7(2.8%)	1(0.8%)	6(5.2%)	0.09
BMI (kg/m²)	29.8 (5.5)	29.84 (6.2)	29.65 (4.6)	0.7
Ejection Fractiona **1** **2** **3** **4**	 204 (87.2%) 20 (8.5%) 6 (2.6%) 4 (1.7%)	 108 (90.8%) 5 (4.2%) 3 (2.5%) 3 (2.5%)	 96 (83.5%) 15 (13%) 3 (2.6%) 1 (0.9%)	0.08
LA size (mm)	41.6 (5.5)	41.5 (5.2)	41.7 (5.7)	0.7
Implanted device				
PPM	23 (9.3%)	4 (3.1%)	19 (16.4%)	<0.001
ICD	6 (2.4%)	1 (0.8%)	5 (4.3%)	0.1

a Ejection Fraction: 1 = Normal = LVEF 50% to 70% (midpoint 60%); 2 = Mild dysfunction = LVEF 40% to 49% (midpoint 45%); 3 = Moderate dysfunction = LVEF 30% to 39% (midpoint 35%); Severe dysfunction = LVEF less than 30%.

Abbreviations: AAD = Anti-Arrhythmic Drug; AF = Atrial Fibrillation; BMI = Body Mass Index; CAD = Coronary Artery Disease; HCM = Hypertrophic Cardiomyopathy; ICD = Implantable Cardioverter Defibrillator; Ischemic CM = ischemic cardiomyopathy; LA = Left Atrial; PAF = Paroxysmal Atrial Fibrillation; PPM = Permanent Pacemaker

Table 2: Previous studies reporting on fluoroless catheter ablation for atrial fibrillation

Study	No. of fluoroless ablations	Setting	Study design	Type of AF	3D mapping system	Utilization of ICE	Energy usage	Patients with cardiac devices (%)	Procedure duration (min)	Complications
Ferguson et al. (2009) [11]	n = 21 No control group	USA	Cohort study, Prospective	PAF + PeAF	Yes (EnSite NavX)	Yes(100%)	RF	NA	208 (188 to 221)	
Reddy et al. (2010) [12]	n = 20 No control group	USA	Cohort study, Prospective	PAF	Yes (EnSite NavX)	Yes (100%)	RF	15	244 ± 75	
Bulava et al. (2015) [9]	Zero-fluoro group, n = 40 Traditional group (Control), n = 40	Czech Republic	Single-center RCT	PAF	Yes (CARTO)	Yes (45%)	RF	NA	92.5 ± 22.9	
Sánchez et al. (2016) [19]	n = 56 No control group	USA	Cohort study, Retrospective	PAF + PeAF	Yes (EnSite NavX)	Yes (70.4%)	RF	10	126 ± 50	
Percell et al. (2016) [20]	n = 20	USA	Cohort study, Retrospective	PAF + PeAF	Yes (EnSite Precision or CARTO)	Yes (100%)	RF or cryoballoon	NA	210	Tamponade (1.2% in the fluorless group)
Razminia et al. (2017) [13]	n = 186 No control group	USA	Cohort study, Retrospective	PAF + PeAF + longstanding PeAF	Yes (EnSite NavX or CARTO)	Yes (100%)	RF or cryoballoon	10	194.4	2 pts with tamponade, 1 pt with atrioesophageal fistula
Liu et al. (2018) [21]	Zero-fluoro group, n = 200 Traditional group (Control), n = 50	USA	Cohort study, Retrospective	PAF + PeAF	No	Yes (100%)	RF	9.5	90.3 ± 17.7	1 pt with partial phrenic palsy, 1 pt with pseudoaneurysm
Lyan et al. (2018) [15]	Zero-fluoro group, n = 245 Traditional group (Control), n = 236	Russia and Kazakhstan	Cohort study, Retrospective	PAF	Yes (CARTO)	Yes (100%)	RF	2.4	108.8 ± 18.2	3 pts with tamponade in the Fluoroless group
Sommer et al. (2018) [14]	n = 1000 No control group	Germany	Clinical Registry	PAF + PeAF + longstanding PeAF	Yes (EnSite Precision)	No	RF	NA	120 ± 40.4	Femoral pseudoaneurysm (n= 10), Pericardial effusion (n = 7), arteriovenous fistula (n= 1), phrenic nerve palsy (n= 1), stroke (n= 1)
Cha et al. (2020) [18]	Zero-fluoro group, n = 30 Traditional group (Control), n = 30	South Korea	Cohort study, Retrospective	PAF + PeAF	Yes (CARTO)	Yes (100%)	RF	NA	163.9 ± 59.7	1 pt with pericardial effusion in the Fluoroless group
Salam et al. (2020) [22]	n = 325 No control group	USA	Case series	PAF + PeAF	Yes (CARTO)	Yes (100%)	RF	NA	134.0 ± 30.5	
Zei et al. (2020) [23]	Zero-fluoro group, n = 100 Traditional group, n = 60	USA	Clinical Registry	PAF + PeAF	Yes (CARTO)	Yes (100%)	RF	1	192 ± 37	1 pt with TIA in the Fluoroless group
Jan et al. (2020) [24]	n = 144 No control group	Slovenia	Cohort study, Prospective	PAF	Yes (EnSite NavX or CARTO)	Yes (100%)	RF	NA	175 ± 40	4 pts with pericardial effusion w/o tamponade, 2 pts with pseudoaneurysm of femoral artery, 1 pt with tamponade, 1 pt with transient phrenic nerve injury
Žižek et al. (2020) [25]	n = 451 No control group	Slovenia	Cohort study, Retrospective	PeAF	Yes (EnSite NavX or CARTO)	Yes (100%)	RF	5.4	161 ± 64	6 pts with pericardial effusion, 2 pts with PSA intervention, 1 pt with tamponade, 1 pt with transient phrenic palsy, 1 pt with CIED lead dislocation
Lurie et al. (2020) [16]	Zero-fluoro group, n = 147 Traditional group (Control), n = 176	Canada	Cohort study, Retrospective	PAF + PeAF	Yes (EnSite or CARTO or Rhythmia)	Yes (100 %)	RF	2.7	176 ± 46	2 pts with pericardial effusion or tamponade, 1 pt with atrioesophageal fistula in the Fluoroless group
Present study (2020)	Zero-fluoro group, n = 116 Traditional group (Control), n = 131	Canada	Cohort study, Retrospective	PAF + PeAF	Yes (CARTO)	Yes (100 %)	RF	2	136.85 ± 33.4	1 pt with tamponade in the Fluoroless group

Abbreviations: AF = atrial fibrillation; CIED = cardiac implantable electronic devices; NA = not available; PAF = paroxysmal atrial fibrillation; PeAF = persistent atrial fibrillation; PVI = pulmonary vein isolation; PSA = pseudoaneurysm; RF = radiofrequency; RCT = randomized clinical trial; TIA = transient ischemic attack

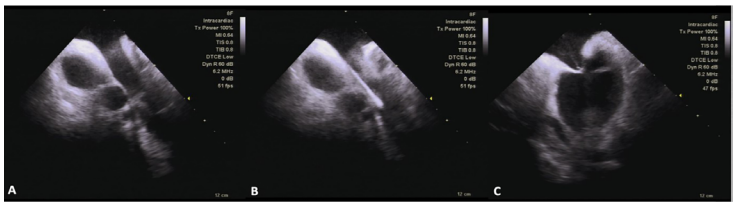

Figure 2: Visualization of superior vena cava (A) and wire in the SVC (B). Tenting of the septum is visulazied (C).

transseptal puncture, catheter stability, and catheter insertions (coronary sinus catheter). However, the LA shell was created with the Lasso catheter. Additionally, the Lasso catheter was used to check the PV isolations at the end of the procedure.

For the traditional fluoroscopy group, the transseptal puncture was performed with ICE and fluoroscopy guidance using standard projections and contrast agents.

Catheters were removed at the end of the procedure, and venous hemostas is was provided by a figure-of-eight suture with a three-way stop cock technique.

Follow up

AF recurrence was defined as any documented episode of AF/atrial tachycardia >30 seconds. The first 90 days (3 months) immediately following the RFA procedure were considered to be the blanking period. Early recurrence was defined as any recurrence of AF/AT in 90 days. Late recurrence was defined as any recurrence at 12 months. Patients were evaluated at the outpatient clinic at 3, 6, and 12 months after the RFA procedure. A 12-lead electrocardiogram (ECG) and 48-hour Holter data were collected. Additional ECG monitoring was instructed if patients exhibited symptoms suggestive of AF. Anti arrhythmic drugs were discontinued in all patients after the blanking period, and oral anticoagulation was continued according to their CHA_2DS_2VASc score.

Statistics

Baseline characteristics were described as mean ±standard deviation for continuous variables and frequencies and percentages for categorical variables. Comparisons between the zero-fluoro and traditional groups were made using the Student's t-test or using the chi-squared test or their non-parametric counterparts, as appropriate. Kaplan Meier analyses were performed to analyze the survival free from early and late arrhythmia recurrence and to compare arrhythmia recurrence between patients in the zero-fluoro and traditional groups during follow-up. Cox proportional-hazards models were developed to compare the risk of early and late recurrence of arrhythmia between the two groups during follow-up. All models were adjusted for age, gender, left atrial diameter, ejection fraction, body mass index, and comorbidities regardless of their significance in the univariate model. All statistical analyses were performed using R Studio (Version 1.2.5042) and R version (Version 4.0.3) with two-sided statistical significance set at an alpha = 0.05.

Results

Population demographics

Overall, 247 patients with AF who underwent PVI for AF were studied. The mean age was 62.2± 10.6 years;60.7% were male, and 63.1% had PAF. ICE-guided PVI without fluoroscopy (Zero-fluoro group) was performed in 116 patients (47%), and conventional fluoroscopy-guided PVI (Traditional group) was performed in 131 patients (53%). Baseline characteristics of the population are summarized in Table 1. The mean fluoroscopy time in the traditional group was 12.5 ± 9.8 minutes. Patients in the traditional group had more permanent pacemakers compared to the zero-fluoro group (16.4% vs. 3.1%; p = <0.001). Otherwise, there were no significant differences in baseline characteristics before ablation between the groups. A chronological description of similar studies describing Fluoroless RFA of AF is depicted in Table 2.

Procedural outcomes

ICE was used in all patients. Initial rhythm, site of ablation, and need for direct current cardioversion post-RFA were similar between both groups. In all cases, RFA was successfully performed. Procedure-related details are summarized in Table 3. Mean procedure times were similar between both groups (136.8 ± 33.4 minutes in the zero-fluoro group vs. 144.3 ± 44.9 minutes in the traditional group; p = 0.2) (Figure 3).

Adverse events

There were no significant differences between complication rates, including hematoma and tamponade, between both groups. The incidence of hematoma was 1 (0.8%) in the zero-fluoro group compared to 4 (3.4%) in the traditional group (p = 0.2). Moreover, the incidence of tamponade was 1 (0.8%) in the zero fluoro group and none in the traditional group (p = 1). The one tamponade in the zero-fluoro group occurred during LA ablation, likely due to a steam pop in the anterior aspect of the RSPV. No other complications occurred in this group.

Recurrence

Survival from early AF recurrence was 85% and 81% in the zero-fluoro and traditional groups, respectively (p=0.06) (Figure 4). Twelve-month survival rates from late AF recurrence were 50% in the zero-fluoro group and 68% in the traditional group, respectively (Figure 5). Moreover, survival from late AF recurrence (12-months) in the zero-

Table 3: Procedural details of patients undergoing traditional and zero-fluoroablation of atrial fibrillation.

	Total	Zero-fluoro	Traditional	P-Value
General Anesthesia	140(57.4%)	104(79.4%)	36(31.9%)	<0.001
Initial Rhythm				0.9
SR	175(71.7%)	92(70.8%)	83(72.8%)	
AT	4(1.6%)	2(1.5%)	2(1.8%)	
AF	65(26.6%)	36(27.7%)	29(25.4%)	
Additional lesion delivery				
LA Roof Line	4(1.6%)	0(0%)	4(3.5%)	0.1
LA Posterior Wall	5(2%)	1(0.8%)	4(3.5%)	0.3
Mitral Isthmus	2(0.8%)	0(0%)	2(1.7%)	0.4
Concurrent AFL	4(1.6%)	0(0%)	4(3.5%)	0.1
DCC Post procedure	111(44.9%)	55(42%)	56(48.3%)	0.3
Procedure duration, min	140.5 ± 39.1	136.8 ± 33.4	144.3 ± 44.9	0.2

Abbreviations: AF = Atrial Fibrillation; AFL = Atrial Flutter; AT = Atrial Tachycardia; DCC = Direct Current Cardioversion; ICE = Intracardiac Echocardiography; LA = Left Atrial; SR = Sinus Rhythm

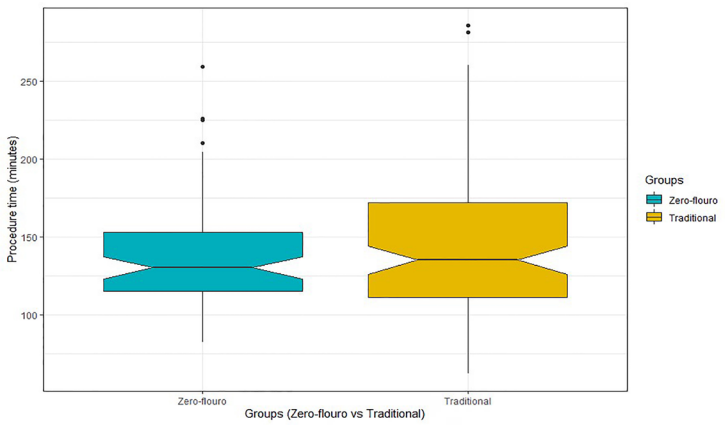

Figure 3: **Box plot of the total procedure time between zero-fluoro and traditional AF ablation groups.**

fluoro and traditional groups were not significantly different (p=0.1).

A Cox proportional-hazards multivariate analysis of the variables, including age, gender, type of AF (PAF vs. persistent AF), presence of hypertension, diabetes, left atrial size, left ventricular ejection fraction, and body mass index showed no significant differences in the risk of early and late AF recurrence (12-months) between the zero-fluoro and traditional groups during follow-up (Traditional vs. Zero-fluoro: early recurrence: Hazard ratio (HR) = 1.7[0.9-3.2], late recurrence: HR0.5[0.2-1.02]).

Discussion

In this single-center study of a local Canadian community, we showed that zero-fluoroscopy RFAhad similar efficacy and safety profiles compared to the traditional fluoroscopy-guided approach. Furthermore, the procedure duration between zero-fluoroscopy and traditional groups was comparable. Freedom from AF was also comparable between both groups. In this study, we showed the safety and feasibility integration of imaging (ICE and CartoSound) and EGM guidance in order to perform fluoroless catheter ablation in patients with PAF and persistent AF.

An increasing number of studies have recently reported on the feasibility and safety of zero-fluoroscopy AF ablation (Table2). Ferguson et al.first demonstrated this technique in 21 patients with AF usingrotational ICE and 3D mapping. The mean procedure duration was 208 minutes, and there were no complications[11].This was followed by Reddy et al.,who described a series of 20 consecutive patients who underwent PVI for PAF using zero-fluoroscopy. The procedure duration was 244 ± 75 minutes, with 97% acute procedural success[12]. The only randomized clinical trial to compare the nonfluoroscopic approach with the traditional approach was performed in 80 patients with PAFin a single-center experience. The authors found no differences in the procedural outcomes or overall safety between the two groups [9]. Most of these studies have been limited by their small scale or a predominant focus on acute procedural outcomes. Razminia et al. reported 5-year experience of zero-fluoroscopy ablation by using ICE and the Ensite system and demonstrated that it was feasible and safe [13]. The largest study employing zero-fluoroscopy during AF ablation was conducted by Sommer et al. with their experience of 1,000 patients treated without fluoroscopy with the Mediguide system [14]. ICE was not used to guide the procedure. Another large-scale study reporting on the long-term safety and efficacy following fluoroless AF ablation retrospectively reviewed 481 consecutive patients with PAF[15]. These authors compared ICE-guided PVI (n = 245) with conventional fluoroscopy-guided PVI (n = 236) and reported no differences in procedural outcomes, complication rates, and AF recurrence. Based on this evidence, zero-fluoroscopy AF ablation utilizing ICE and 3D mapping appears to be feasible, safe, and effective compared to fluoroscopy-guided ablation. Our cohort included 247 consecutive patients with PAF or persistent AF and included 131 patients in the fluoroscopy-guided RF ablation group and 116 patients in the zero-fluoroscopy ablation group. CARTO 3D mapping was utilized during all our procedures. Lurie et al. recently detailed their first-ever Canadian experience with 323 consecutive AF patients. Of these, 176 patients were treated with fluoroscopy-guided RF ablation, and 147 patients were treated with zero-fluoroscopy ablation and utilized3D mapping systems (EnSite, n = 175; CARTO, n = 144; Rhythmia, n = 3). Minimal fluoroscopy was used in 17 patients in the zero-fluoroscopy group (median 3 seconds, IQR 1.2 – 4.8)[16]. Both studies (Lurie et al. and our cohort) included patients with cardiac devices as well. In comparison with other previous studies, our cohort revealed high acute procedural success rate of 100%, a complication rate of 0.9%, and aprocedure duration of 136.85 ± 33.4 minutes. The low complication rate with the zero-fluoroscopy technique may be due to visualizing the guide wires and the catheters while advancing into the heart to avoid injuries.

It has been reported that the learning curve for zero-fluoroscopy AF ablation occurs over the first 20 cases [17]. For an experienced operator, zero-fluoroscopy AF ablation might be achieved safely and feasibly within 5 to 10 cases [18]. Our recommendation, based on experience, is for operators with less experience to avoid Fluoroless AF ablation in patients with cardiac devices in order to prevent any inadvertent lead

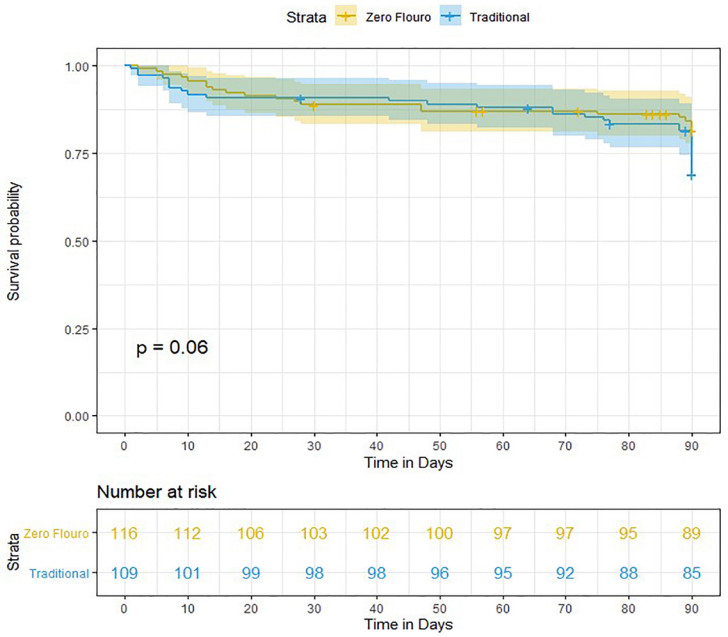

Figure 4: **Survival curve for early recurrence of AF in the zero-fluoro and traditional groups**

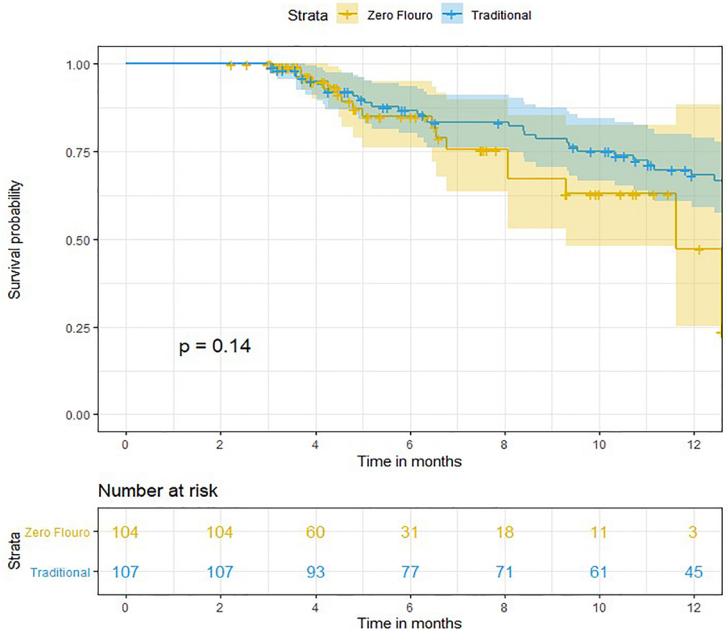

Figure 5: **Survival curve for late recurrence of AF in the zero-fluoro and traditional groups.**

issues such as dislodgement. Operators experienced in the utilization of ICE may not view this as a limitation. We believe that if the operators perform zero-fluoroscopy procedures as routine practice, adverse effects of ionizing radiation could be significantly reduced in both patients and the medical staff.

Limitations

The study was performed by a single operator at a single center, and therefore results of this study may not be applicable to other centers. For context, three operators perform around 450 to 500 AF ablations a year; however, only one operator in the practice performs Fluoroless AF ablation. Another limitation was our study's retrospective and nonrandomized design. There were very few patients with cardiac devices in the zero-fluoroscopy arm; therefore, more data are required before adopting a zero-fluoroscopy approach in patients with cardiac devices. Detailed procedure measures such as time to transseptal puncture and left atrial dwell time were not recorded, which could differ between zero-fluoroscopy and traditional groups. Another limitation was that an esophageal temperature probe (Smiths Medical, Minneapolis, MN, USA) with a single sensor was used. Only one point was marked on the map. This may not be sufficient since the esophagus has a longer course. Lastly, this technique may not be adaptable to other mapping systems as the CARTOSOUND® Module with SOUNDSTAR® Catheter are only compatible with CARTO® 3 System and proprietary to Biosense Webster.

Conclusion

Fluoroless RFA was associated with similar safety and efficacy profiles as the traditional AF ablation. In addition, AF ablation without fluoroscopy did not prolong the total mean procedure time or compromise the recurrence rate during long-term follow-up.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Please Click for Supplementary Appendix

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Contact-Force Guided Posterior Wall Isolation as an Adjunctive Ablation Strategy for Persistent Atrial Fibrillation

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Abstract

Background: The efficacy of posterior wall isolation (PWI) on top of pulmonary vein isolation (PVI) in patients affected by persistent atrial fibrillation (AF) is still controversial and little is known about the impact of contact-force (CF) technology.

Objective: In this retrospective study, we present our experience with PWI using CF sensing catheters and its efficacy and safety as an adjunctive ablation strategy on top of PVI for management of patients with persistent and longstanding persistent AF.

Methods: A total of 73 consecutive patients (20.5% female) affected by persistent atrial fibrillation (10.9% long-standing) underwent PWI as an adjunctive therapy to PVI using CF sensing catheters. Outcomes were reported as incidence of atrial arrhythmic recurrences (ARs) lasting >30 seconds at follow up and in addition, in patients provided with insertable cardiac monitors (ICM), as burden of AF or atrial tachycardias (AT) at relevant time points.

Results: PWI was successfully achieved in 65 (89.0%) patients. Two (2.7%) minor vascular procedural complications were observed. At 1 and 2-year follow-up, ARs free survival was observed in 80.5% and 64.1% of patients, respectively with 75.3% of patients off antiarrhythmic drugs at the last follow-up. Ten patients underwent repeat ablations during the follow-up. At multivariate analysis, early ARs within 3 months after procedure, were associated with a two-fold increased risk of late ARs at follow-up. Among patients provided with ICM, PWI on top of PVI was able to reduce the mean AT/AF burden of more than 50% compared with pre-ablation time, reporting very low levels (≤ 5%) over 2 years.

Conclusions: In persistent atrial fibrillation, PWI on top of PVI using CF sensing catheters is safe and effective, providing great reduction of burden of ARs. Early ARs are associated with a greater risk of late recurrences.

Introduction

Pulmonary vein isolation (PVI) is currently recommended for paroxysmal atrial fibrillation (AF) catheter ablation, but persistent AF remains a clinical challenge [1-3]. In this setting, guidelines recommend that substrate modification should be considered on top of PVI, but the technical approach is not univocally defined and various strategies have been proposed [1,2,4]. Among strategies to achieve atrial compartmentalization and de-bulking, posterior wall isolation (PWI) allows the reduction of LA critical mass and also the suppression of AF triggers and drivers [5]. Percutaneous PWI derives from the Cox maze IV surgical procedure [6] and it may be achieved by creating a roof line together with a line, close to the floor of the LA, joining the lower borders of the inferior pulmonary veins on top of PVI [7]. PWI seems to be an alternative option in persistent AF treatment, though technically demanding, uncertain in terms of arrhythmic recurrences (ARs) [8,9] and burdened by a great incidence of reconnections at follow-up [10,11]. Contact-force (CF) technology was not, however, routinely used in previous prospective studies on percutaneous PWI, even if it provides deeper and more durable lesions when integrated in ablation

Key Words

Persistent Atrial Fibrillation, Posterior Wall Isolation, Contact Force, Early Recurrence, AF Burden.

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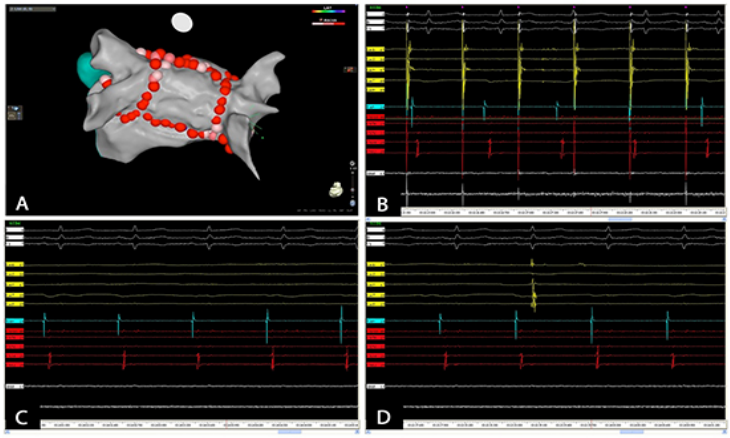

Figure 1: Following PVI, PWI is performed with roof and floor lines (panel A). PWI is validated with pacing maneuvers within the posterior wall showing electrical dissociation from left atrium (panel B). Electrical block is also validated by evidence of absence of local potential (panel C) and/or appearance of a dissociated potential within the posterior wall (panel D).

catheters either in paroxysmal or in persistent AF ablations [12-14]. In this retrospective study, we present our experience with PWI using CF sensing catheters and its efficacy and safety as an adjunctive ablation strategy on top of PVI for management of patients with persistent and longstanding persistent AF.

Methods

Study population

Consecutive patients with symptomatic and drug-refractory persistent or long-standing persistent AF who underwent CF supported PWI on top of PVI between October 2012 and October 2018 at Istituto Clinico Sant'Ambrogio (Milan, Italy) were retrospectively analysed. All data were obtained by review of the electronic medical records and any incongruent data was appropriately evaluated by two independent reviewers. Persistent AF was defined as AF episodes lasting longer than 7 days but less than 1 year. Longstanding persistent AF was defined as AF lasting longer than 1 year 1. Prior catheter ablations did not represent an exclusion criterion, unless ablation strategies other than PVI were included in their prior procedures. To assess the confounding impact of previous ablations on the interpretation of our results, we additionally performed sub-analyses of our data dividing our cohort in two groups according to whether PWI was performed on first or repeat ablation and reported results as appropriate. Patients who had less than 3 months of follow-up post procedure were excluded from the analysis. Demographic data and baseline characteristics were collected in all patients. The study protocol adhered to the Declaration of Helsinki and was approved by our institutional Review Board.

Catheter ablation procedure

AF radiofrequency catheter ablations were performed by 4 experienced cardiac electrophysiologists using standard protocols. All procedures were undertaken under general anaesthesia and after the exclusion of the presence of an intracardiac thrombus with an intraoperative trans-oesophageal echocardiographic exam. All patients received intravenous unfractioned heparin with a target Activated Coagulation Time (ACT) of 350-400 sec. Using a single transfemoral venous access and a single transseptal puncture, a circular mapping catheter (Lasso® Catheter, Biosense Webster or Reflexion SpiralTM, Abbot Laboratories) and a 3.5-mm open-irrigated-tip CF supported ablation catheter (Thermo Cool® Smart Touch® Biosense Webster or TactiCathTM Abbot Laboratories) were positioned in the LA. Catheter ablation was assisted by 3D mapping with image integration (NavX velocity, Abbot Laboratories or CARTO3, Biosense Webster). In all patients PVI was performed by creating a wide antral ablation line around each pair of ipsilateral pulmonary veins with point-by-point RF delivery. Ablation in the carina segments was optional. In case of repeat procedures, only pulmonary veins with evidence of electrical re-connections were isolated. Following PVI, PWI was performed with 'roof line' at the most cranial aspect of the LA, followed by 'floor line' joining the most inferior margin of the inferior pulmonary veins (Fig.1A). Ablations were performed with point-by-point tags until separation or attenuation of the local electrogram limiting power to 30-35 W for anterior wall and 25-30 W for posterior wall. Ablation targets were points showing local CF values comprised between 10 g and 40 g. In patients with persistent AF at the end of the procedure, sinus rhythm was restored using external cardioversion. Electrical disconnection between pulmonary veins and LA was validated with circular mapping catheter positioned at the ostia of the respective PVs. Endpoint of the procedure was complete isolation of the posterior wall that was validated by positioning the circular mapping catheter in the mid-posterior wall of LA. Electrical block was validated by pacing from posterior wall showing local capture and exit block to the remainder of the atrium (Fig. 1B) or by showing absence of local potential and/or the appearance of a dissociated potential (Fig.1C and 1D). If further atrial flutter or focal atrial tachycardia (AT) were observed, mapping and ablation were performed as appropriate. Persistency of PVI and PWI was confirmed at 30 minutes from the beginning of the ablation. Atrial bursts aimed at testing AF inducibility were performed at the end of the procedure. Cavo-tricuspid isthmus ablation was performed in patients who had history of typical atrial flutter. An oesophageal temperature probe (Esotherm, FIAB Spa, Firenze, Italy) was used in all patients and radiofrequency delivery was interrupted for temperature elevations greater than 40 °C. Radiofrequency, fluoroscopy and procedural times

Table 1: Baseline characteristics

	Study population (n = 73)
Mean age (yr)	60.9 ± 10.0
Females, n (%)	15 (20.5)
AF duration (years from diagnosis)	2.1 ± 1.3
Longstanding persistent AF, n (%)	8 (10.9)
Previous ablation in LA (PVI), n (%)	48 (65.7)
Number of tested AAD	1.4± 0.6
Hypertension, n (%)	41 (69.8)
Diabetes, n (%)	10 (13.6)
CAD, n (%)	7 (9.6)
Previous stroke or TIA, n (%)	4 (5.5)
LVEF (%)	52.9 ± 8.5
LA diameter (mm)	45.6 ± 5.5
ICM, n (%)	32 (43.8)

All values represent mean±standard deviation or number and (percentage). AF: atrial fibrillation; AAD: anti arrhythmic drugs; CAD: coronary artery disease; ICM: insertable cardiac monitor; LA: left atrium. LVEF: left ventricular ejection fraction; PVI: pulmonartiy vein isolation; TIA: transient ischemic attack.

Table 2: Procedural variables

	Study population Overall (n = 73)	First ablation group (n=25)	Repeat ablation group (n =48)	p-value
Completion of PWI, n (%)	65 (89.0%)	23 (92.0)	42 (87.5)	0.29
Restoration of sinus rhythm during ablation, n (%)	8 (10.9%)	3 (12.0)	7 (14.5)	0.45
CARTO 3/Navx, n	49/24	16/9	33/15	0.86
Cavo-tricuspid isthmus ablation, n (%)	30 (41.1%)	11 (44.0)	17 (35.0)	0.12
Procedure time (min)*	178.1 ± 40.9	169.1 ± 38.9	152.1 ± 42.9	0.13
Ablation time (min)	44.1 ± 12.4	49.1 ± 18.6	36.2 ± 15.4	0.12
Fluoroscopy time (min)	26.6 ± 13.8	28.3 ± 11.0	22.4 ± 11.7	0.23

All values represent mean±standard deviation or number and (percentage). PWI: posterior wall isolation. *Includes transesophageal echocardiography and administration of general anesthesia and mechanical ventilation.

and incidence of complications were collected for each procedure.

Follow-up and clinical outcomes

Patients received a prescription of pantoprazole (40 mg daily) for 4 weeks after discharge to avoid gastroparesis. Oral anticoagulants were stopped at 3-month of follow-up based on CHA2DS2 VASC-score, while antiarrhythmic drugs (AAD) were withdrawn at 3 months (if prescribed at discharge) or continued at discretion of physician. Routine follow-up assessments were conducted in accordance with a standard protocol at our centre. Follow-up consultations in the outpatient clinic were scheduled at 3, 6, 12 and 24 months after procedure and in any case if needed based on AF-related symptoms. Each follow-up focused on assessment of ARs and AF-related symptoms. AR was defined as any documented episode of atrial arrhythmia (including AF, atrial flutter or AT) lasting longer than 30 seconds and occurring after 90 days after ablation (blanking period). Any AR observed within 3-month after ablation was defined as early AR.

Assessment of ARs was based on 24-h Holter ECG monitoring that was routinely ordered at 3-6-12 and 24 months post procedure and as needed thereafter to assess symptoms. In patients provided with insertable cardiac monitors (ICMs) implanted before procedure, the AR detection was based on continuous monitoring. ICMs included implantable electronic devices (CIEDS) with atrial leads or implantable loop recorders (ILRs). ILRs were most commonly Reveal XT (Medtronic, Minneapolis, MN). The ILRs are able to detect episodes of atrial arrhythmias lasting at least 2 minutes, while for CIEDS individual manufacturer provides specific atrial arrhythmia detection algorithms. ICM was able to provide, over time, the number of arrhythmia episodes, their duration, and, when all durations of AF/AT episodes were added, the AF/AT burden. The AF/AT burden was calculated as the percentage of time in AF/AT between each follow-up visit, based on manually adjudicated episodes. During follow-up, repeat ablations or electrical cardioversions and/or drug adjustment were performed based on documented and clinically relevant ARs beyond the 'blanking period' and on clinical judgement.

Statistical analysis

Continuous variables are summarized as mean ± standard deviation (SD), whereas categorical variables as count and percentages. Statistical differences between the two groups were assessed with a t-test for continuous variables and a Chi-squared or Fisher's exact test for categorical variables, respectively. Incidence of ARs were estimated using the Kaplan–Meier method for the entire cohort and log-rank test was performed to present and compare survivals in first and repeat ablation groups. A Cox hazard regression analysis was performed to determine predictors of ARs. All parameters that had a suggested association with recurrence by univariate analysis (P <0.1) were included in a stepwise regression analysis, and the results were reported as hazard ratios (HR) with 95% confidence intervals (CIs). All data were analysed using SPSS statistical software, version 22.0 (IBM Corp., Chicago, IL, USA). A two-sided P value ≤ 0.05 was considered statistically significant.

Results

Study population

After exclusion of 8 patients who had undergone previous either surgical o percutaneous PWI, 10 patients who experienced previous linear ablations in LA (roof and anterior lines) and 1 patient with less than 3 months of follow-up, 73 patients were included in this study. Baseline characteristics of the study population are presented in Table 1. The mean age was 60.9±10.0 years and 8 (10.9) patients presented long-standing persistent AF. PWI was performed on a repeat procedure in 48 patients (65.7%), who had previously undergone PVI. AF duration prior PWI was longer in patients with history of previous ablation than in those at first procedure (2.8 ± 1.3 vs 1.5 ± 1.2, p=0.04). ICMs, which included 29 loop recorders, 2 pacemakers and 1 cardiac defibrillator, were present in 32 (43.8%) patients.

Catheter ablation procedure

Table 2 shows procedural characteristics for the entire population and additionally for two groups divided according to the history of previous ablation (first and repeat ablation groups). PVI was acutely achieved in all patients. PWI was acutely completed at index procedure in 65 (89.0%) patients, while remaining patients showed insuperable oesophageal temperatures (greater than 40°C). Reversion to sinus rhythm during ablation occurred in 8 (10.9%) patients. In repeat ablation group, 9 out of 48 (18.7%) patients showed reconnections in at least one pulmonary vein that were re-isolated as appropriate. Average CF per ablation lesions at all sites was 17.4 ± 3.7 g. Average CF per ablation lesion was 13.2 ± 3.7, 18.2 ± 4.7, 18.2 ± 4.2 and 20.2 ± 2.7 g at the anterior aspect of the right and left pulmonary veins sites, at roof and posterior wall sites, respectively. The average procedure duration

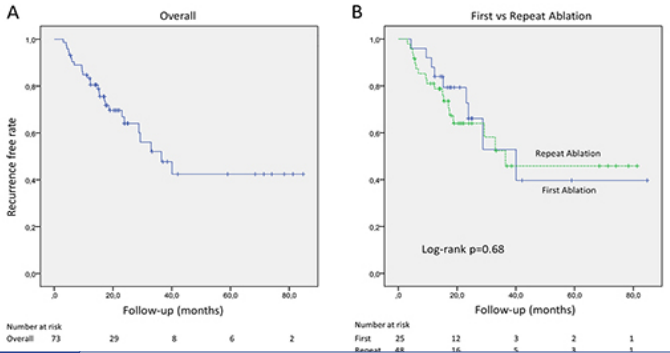

Figure 2: Kaplan-Meier curves show arrhythmia-free survivals associated with PWI on top of PVI in overall population (panel A) and in patients grouped according to the history of previous ablations (PVI) (panel B).

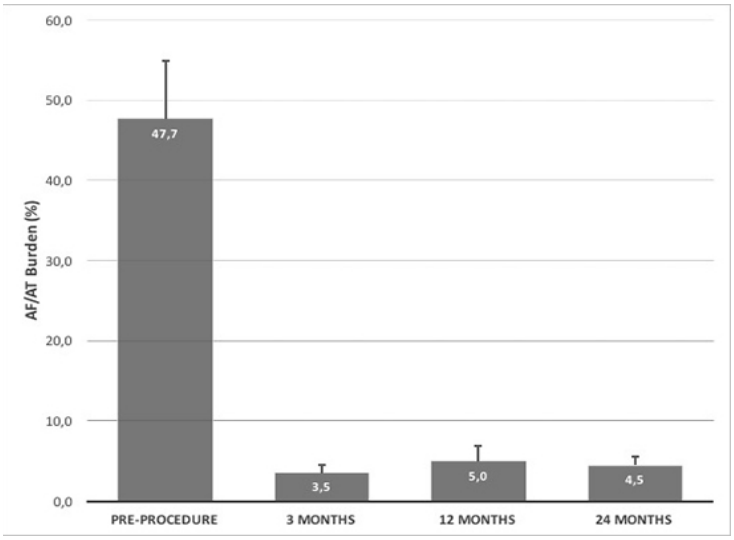

Figure 3: The graphic shows AF/AT burdens detected by ICMs at different time points: prior to ablation, at 3,12 and 24 months following PWI on top of PVI. All values represent mean + standard deviation.

was 178.1±40.9 min. No differences in procedural characteristics were observed between first and repeat ablation groups. With respect to complications, we observed 1 femoral artero-venous fistula and 1 femoral pseudoaneurysm conservatively treated and equally distributed in first and repeat ablation groups.

Follow-up and clinical outcomes

Patients were followed for a mean follow-up of 28.2 ± 2.7 months. At the end of follow-up period, total ARs were 27 (30.1%), of which 21 were AF, 5 were atrial flutter and 1 was AT. In 55 patients (75.3%) AAD were withdrawn at the end of the 90-day blanking period. Among patients experiencing ARs, 8 patients required elective cardioversion outside the blanking period and 10 patients underwent a repeat ablation during the follow-up (1 for AT, 4 for atrial flutter, 5 for AF). Of them, 4 patients presented incompleteness of PWI at endocardial mapping. Among 8 patients with incomplete PWI at index procedure, 3 patients experienced ARs at follow up, with 2 patients treated with repeat ablations and 1 with drug adjustment.

At 1 and 2-year follow-up, freedom from ARs was observed in 80.5% and 64.1% of patients, respectively. The Kaplan-Meier estimates of freedom from any ARs across the entire cohort is shown in Figure 2A. At sub analysis of the data according to the history of previous ablations, 9 (36.0%) and 18 (37.5%) ARs were observed in first and repeat ablation groups, at the end of follow-up, respectively. AR free survival curves are shown for the two groups in Figure 2B, reporting no differences between groups at one-year (84.0% vs 81.0%) and two-years (66.1% vs 64.0%) of follow-up, log-Rank p = 0.68 (Fig. 2B).

Table 3 shows results of Cox hazard regression analyses concerning potential factors associated with risk of ARs after blanking period at follow-up. Previous ablation was not associated with risk of recurrence, while occurrence of early ARs during blanking period was independently associated with incidence of ARs at follow-up (HR 2.47, CI 0.99-6.15, p=0.04). In addition, the achievement of complete PWI during the index procedure demonstrated a favorable effect in averting recurrences at follow up (p=0.08), however statistical significance was not reached.

Among 32 patients provided with ICMs, PWI on top of PVI was able to significantly reduce the mean burdens of ARs (more than 50%) compared with time prior PWI+PVI procedure, reporting levels ≤ 5% at 3, 12 and 24 months after index procedure (Fig.3).

Discussion

In this study, we reported efficacy and safety at 1 and 2 years follow-up of PWI on top of PVI on persistent and long standing persistent AF patients when performed with CF sensing catheters. We showed that early recurrences within 90 days after procedure were associated with a two-fold increased risk of ARs at follow-up. Furthermore, we reported that CF supported PWI +PVI provided great and persisting reduction of burden of ARs over time.

The posterior wall or 'pulmonary venous component' of the LA seems an attractive target for ablation, since there is anatomic and electrophysiological evidence that it contributes to the genesis and maintenance of AF [5]. Furthermore, the posterior wall is a part of the critical mass necessary to maintain AF and so debulking the LA through PWI can reduce AF burden [15]. Despite PWI has not been shown to have additional benefit to PVI in paroxysmal AF [16], it can reduce arrhythmia in persistent AF, as reported in previous studies, however data are still conflicting [8,9]. CF sensing catheters are known to be associated with deeper and more durable lesions either in paroxysmal [12,13] or, as recently reported, in persistent AF ablations [14] and are nowadays advisable also for safety concerns. Actually, real-time CF assessment helps in detection of excessive pressures during ablation, thus avoiding dangerous overtreatments.

The role of CF technology in efficacy and safety of PWI on top of PVI has not been deeply investigated in prospective trials, but a retrospective study demonstrated the superior efficacy of PVI plus PWI using CF sensing compared with standard radiofrequency ablation catheters for patients with persistent AF [17]. In this study, the reported 12 months rates of freedom from ARs were 85% vs 70% in CF vs non-CF group, respectively. However, the authors investigated the role of non-PV triggers ablation in addition to PWI on top of PVI, providing a potential bias in the analysis of the results. In our study, we analysed only procedures where PWI was firstly attempted on top

Table 3: Cox hazard regression analyses of the risks of arrhythmic recurrences

	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	0.99 (0.95-2.79)	0.91		
Females	1.09 (0.41-2.91)	0.85		
Previous ablation in LA (PVI)	0.50 (0.21-1.19)	0.12		
LVEF < 40%	2.73 (0.64-7.6)	0.17		
LA diameter > 40 mm	1.19 (0.47-2.99)	0.70		
Complete PWI	0.42 (0.16-1.11)	0.08	0.41 (0.15-1.16)	0.08
Early AR	2.45 (0.98-6.10)	0.05	2.47 (0.99-6.15)	0.04

AR: arrhythmic recurrence; LA: left atrium; LVEF: left ventricular ejection fraction; PVI: pulmonary vein isolation; PWI: posterior wall isolation; HR: hazard ratio; CI: confidence interval

of PVI, without targeting additional ablation strategies. Furthermore, we evaluated incidence of ARs at longer follow-up period (2 years). In our study, arrhythmias-free survivals at 1 and 2-year follow-up of PWI on top of PVI performed with CF sensing catheters were 80.5% and 64.1% respectively, with 75.3% of patients free from AAD at follow up. A recent randomized trial reported a 73.5% freedom from ARs on and off AAD after PWI in addition to PVI after a mean follow-up of 16.2±8.8 months without the routinely use of CF sensing [18]. Based on our results, routine use of CF sensing catheters while performing PWI might ameliorate efficacy of PWI in terms of incidence of ARs at follow up.

With respect to predictors of recurrence, we found that occurrence of early ARs during blanking period was independently associated with risk of ARs at follow-up. This association was previously reported in literature for different ablation strategies in AF [19,20]. In our series, we reported for the first time that detection of early ARs during blanking period is associated with a 2-fold increased risk of late recurrences after PWI+PVI. It is possible that inflammatory response related to ablation might favor early irritability in LA after ablations and, consequently, the incidence of early ARs soon after the ablation. Based on that, it could be speculated that PWI on top of PVI is associated with more extensive myocardial damage and greater inflammatory response than PVI alone, influencing the incidence of early ARs. However, in a randomized study, Kim et al. showed that levels of hs-CRP, CK-MB and troponin-T were similar in PVI alone and PVI+PWI groups after ablation, proving that inflammatory response and myocardial injury are not increased PWI on top of PVI procedures compared with PVI alone [21]. The relatively high proportion of patients (43.8%) provided with continuous monitoring in our cohort favored a more accurate detection of arrhythmic events, reinforcing this result.

Furthermore, we reported that complete PWI during the index procedure provided a favorable effect in averting recurrences at follow up, despite on our small sample size statistical significance was not reached. Similarly, Kim et al. previously reported that acutely achievement of PWI is a strong predictor of ARs at follow up in a randomized study including patients undergoing PVI+PWI [21]. However, in another observational study PWI incompleteness at index procedure did not impact the outcome [22]. Nevertheless, documented complete posterior wall electrical dissociation is generally the main endpoint of the procedure. It is out of doubt, however, that completeness of PWI is often challenging and, even with meticulous point by point linear ablations, residual gaps often persist [10,11]. In our study, the incompleteness of PWI was observed only in cases where radiofrequency power delivery was reduced or stopped due to excessive temperatures detected at the intraluminal oesophageal probe and not for insuperable technical difficulties. Based on our retrospective analysis, CF sensing catheters supported the operator in achieving complete PWI, however larger and prospective studies are needed to evaluate the role of CF sensing catheters on such procedural endpoint during PWI execution.

With respect to patients who underwent previous PVI before performing PWI, repeat ablation was not associated with risk of ARs at follow up, as previously reported [22]. As expected, patients undergoing PWI on a repeat ablation showed longer AF history compared with patients who underwent ablation for the first time. On the other hand, procedural times and complication rates were similar in the two groups. The inclusion of patients with history of previous ablation in our study can be questionable, as it introduces a possible source of confounding factors. However, the aim of our study was to describe the routine clinical practice of our centre between 2012 and 2018, where persistent AF patients underwent PWI as an adjunctive strategy more frequently after failure of previous PVI strategy than at a first ablation procedure.

Finally, in patients provided with ICMs, our data reported an important reduction of AF/AT burden after PWI on top of PVI compared with burden at time prior to ablation and this data persisted over time. Our data showed that AF/AT burden was reduced at very low levels (≤5%), if compared with CABANA trial and STAR-AF II trial sub-studies, where reported AF/AT burdens at 12 months after AF ablations were 6.3% and 6.8%, respectively [23,24]. AF/AT burden after ablation seems to provide better assessment of outcome of AF catheter ablation, when compared with conventional definition of AF ablation success (occurrence of any AF/AT or flutter lasting >30 seconds), because it is based on clinically relevant recurrences compared with the absolute freedom from recurrence [25]. In this regard, patients undergoing PWI are generally the most challenging ones, presenting with persistent AF, multiple previous ablations and disabling AF related symptoms for many years. In this context, as AF ablation success rate is currently unsatisfactory [3], AF/AT burden reduction could be a desirable target and, based on our results, PWI could play an important role. However, further studies are needed aimed at evaluating the success rate of PWI on top of PVI based on continuous monitoring in all patients.

Limitations of the study

The major limitation of this study is the absence of a comparator group. Although our data suggest that CF sensing catheters can achieve reduction in ARs and durably low AF/AT burden in patients with persistent AF, we are not able to comment on whether similar outcomes may be achievable without CF supported PWI. Furthermore, the retrospective nature of the study and the small sample size limit the power of the analysis. Another limitation is that a great number of patients (65.7%) underwent CF guided PWI after previous ablation in LA, that could be a confounding factor in efficacy and safety assessment of PWI on top of PVI. However, only PVI-based ablations performed before the PWI index procedure were included in the analysis. To assess the weight of this possible confounding factor on our results, we performed sub-analyses of our data dividing our cohort in two groups according to the history of previous ablations and we found no significant differences in procedural results and follow-up outcomes. Another limitation of this study is that AF burden data, provided at ICMs analysis, were derived from less than 50% of patients of our population, reducing the power of our conclusions.

Conclusions

CF supported PWI on top of PVI in persistent AF ablation was as effective as safe at 1 and 2 years of follow-up. Early ARs during blanking period predicted the incidence of late recurrences at follow-up. PWI on top of PVI provided significant and persistent AF/AT burden reduction over time. Prospective studies aimed at evaluating the efficacy of PWI on top of PVI using CF sensing catheters with lesion detecting tools and ICMs as monitoring systems in all patients are advisable.

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Incidence and Prognostic Impact of New-Onset Atrial Fibrillation in Patients with Severe Covid-19: A Retrospective Cohort Study

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Abstract

Background: Corona virus disease 2019 (COVID-19) contributes to cardiovascular complications including arrhythmias due to high inflammatory surge. Nevertheless, the common types of arrhythmia amongst severe COVID-19 is not well described. New onset atrial fibrillation(NOAF) is frequently seen in critically ill patients and therefore we aim to assess the incidence of NOAF in severe COVID -19 and its association with prognosis.

Methods: This is a retrospective multicentre study including 109 consecutive patients admitted to intensive care units (ICU) with confirmed COVID-19 pneumonia and definitive outcome (death or discharge). The study period was between 11th March and 5th May 2020.

Results: Median age of our population was 59 years (IQR 53-65) and 83% were men. Nearly three-fourth of the population had two or more comorbidities. 14.6% developed NOAF during ICU stay with increased risk amongst older age and with underlying chronic heart failure and chronic kidney disease. NOAF developed earlier during the course of severe COVID-19 infection amongst non-survivors than those survived the illness and strongly associated with increased in-hospital death (OR 5.4; 95% CI 1.7-17; p=0.004).

Conclusion: In our cohort with severe COVID-19, the incidence of new onset atrial fibrillation is comparatively lower than patients treated in ICU with severe sepsis in general. Presence of NOAF has shown to be a poor prognostic marker in this disease entity.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread globally causing COVID-19 since the first reported cases in Wuhan, China in December 2019 [1-3].The majority with COVID-19 remain asymptomatic or with mild symptoms, however around 20 % will have severe symptoms with multiorgan failure triggered by cytokine storm[4]. Several recent studies have demonstrated the deleterious effects of COVID 19 on cardiovascular system comprising acute myocardial injury, myocarditis, cardiomyopathies, arrythmias, cardiogenic shock and cardiac arrest [5-8].

New onset atrial fibrillation (NOAF) is the most comment arrythmia seen in patients treated in intensive care unit (ICU) and is a sequelea of critical illness. The incidence of NOAF is reported between 20-46% amongst patients treated for sepsis in ICU with a strong association with mortality [9-12]. Inflammation per se is likely a trigger for initiation, maintainance and perpetuation of AF [13]. We hypothesized the incidence of NOAF will be higher in COVID-19 due to high in flammatory state secondary to cytokine release syndrome. In a study by Wang et al, arrythmia amongst COVID-19 were more common in ICU patients (44.4%) than the counterpart [14]; however, the nature of the arrythmias was not described.There is paucity in the emerging literatures with regard to the nature of common arrythmias attributed by COVID-19 in ICU and there is no literature so far reporting the frequency of NOAF in severe COVID-19. Therefore the purpose of our study is to explore the incidence and clinical characteristics of patients with NOAF in severe COVID-19 admitted to ICU and to evaluate its prognostic impact with respect to mortality.

Key Words

COVID-19 pneumonia, New onset Atrial Fibrillation, In-hospital mortality.

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Methods

Study design and participants

This is a retrospective multicentre study, encompassing two major COVID 19 ICU centres in London; including St Bartholomew's Hospital and the Nightingale Hospital London, which was the field hospital intensive care unit for COVID-19 during first wave of the pandemic. The study population comprised of consecutive patients (over the age of 18 years) admitted to COVID-19 intensive care units between March 11 - May 5, 2020 definitive clinical outcome

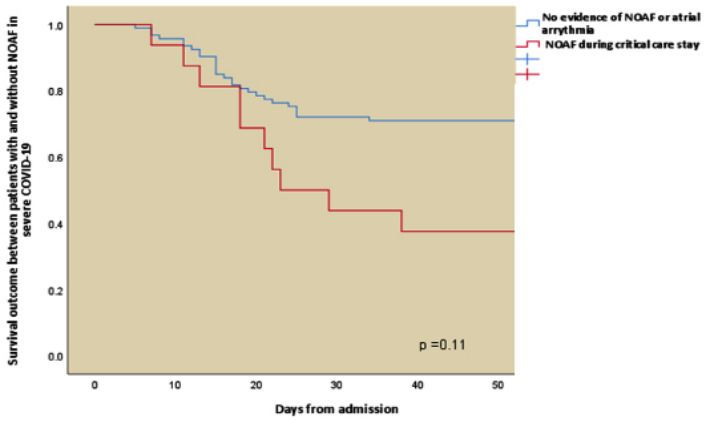

Figure 1: Cumulative incidence curve for survival between patients with and without NOAF during ICU stay.

Higher incidence of mortality was associated with patients with NOAF in severe COVID 19.

either discharge or death. One hundred and thirteen patients [St Bartholomew's Hospital (73) and Nightingale Hospital (40)]were included fulfilling the above criteria, however 4 patients were excluded due to pre-existing diagnosis of permanent or persistent AF.

All patients had a laboratory confirmed diagnosis with detection of SARS-CoV-2 RNA on swab (nasal/throat) results. Demographic, clinical, laboratory and imaging data were extracted from the electronic medical records (Cerner Millennium- registered clinical portal of the institutions) and the details regarding premorbid conditions were also cross referenced with their respective general practitioner's (GP) records.

Definition

In this study NOAF was defined as episodes of paroxysmal or persistent AF occurred during ICU stay with no previous diagnosis of AF. All patients were attached to continuous cardiac monitor and episodes were confirmed on 12 lead electrocardiography. Chronic kidney disease was classified in stages by eGFR according to the KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guidelines. Acute kidney injury was also classed according to the KDIGO clinical practice guidelines.

Acute cardiac injury was diagnosed if serum levels of cardiac biomarker (Troponin T) were above the 99th percentile of the upper reference range and if new abnormalities were shown in echocardiography or electrocardiogram. Patients with heart failure with reduced ejection fraction (HFrEF) as per ESC guidelines (left ventricular ejection fraction less than 40%) were classed under chronic heart failure. The linear dimension (anteroposterior measurement on parasternal long axis view) was taken into consideration for measuring left atrial (LA) size and was categorized according to the reference values from British Society of Echocardiography. Extra corporeal membrane oxygenation (ECMO) was offered to patients with acute severe and potentially reversible respiratory failure despite ventilator support who fulfilled the NHS England ECMO guidelines (version 1- revised in response to the COVID-19 pandemic). All documented diagnoses of pulmonary embolism (PE) were confirmed radiologically following computed tomography pulmonary angiogram (CTPA).The highest value of the laboratory markers prior to the AF episode were taken into account for the purpose of analysis in table 2.

Statistical analysis

Categorical variables were described as frequency (percentage) and continuous variables as median (interquartile range). Continuous and categorical variables were compared using Mann-Whitney U test and the $\chi 2$ test respectively. Fisher exact test was used when the data were limited. Univariate and multivariable logistic regression models were used to explore the association between NOAF with in-hospital mortality. Kaplan-Meire plot was used to assess the survival outcome since admission. A 2-sided α of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) software, version 26.0 software (IBM SPSS Statistics).

Results

The study population included 109 ICU patients with confirmed COVID-19 out of which 107 (98%) required invasive mechanical ventilation and the remainder were treated with non-invasive ventilation.All had radiological evidence of acute respiratory distress syndrome (ARDS) or pneumonia. Out of total, 3 patients (3%) admitted to ICU after been treated for myocardial infarction during the index admission and 2(2%) were diagnosed following cardiac surgery. Primary cause of admission for the rest was symptoms of COVID-19 pneumonia. The median age was 59 years (IQR 53-65; range 30-79 years) and 83% were men. Two or more comorbidities were observed in 72 % of patients (Table 1).

Clinical characteristics during admission

NOAF was found in 16 patients (14.6%) with in this cohort which also includes one post cardiac surgical patient. Clinical characteristics between patients developed NOAF were further studied with comparison to the group of patients without AF. Majority (70 [64%]) had acute kidney injury and of which 36% patients required renal replacement therapy. Major laboratory markers were traced during

Table 1: Baseline Characteristics of patients treated in ICU with COVID-19

	Total (N=109)	With NOAF during ICU stay (n=16)	Without NOAF during ICU stay (n= 93)	P value
Demographics and clinical characteristics				
Age , median (IQR), y	59 (53-65)	65(59-71)	58 (51-64)	0.001
Sex				0.12
Female	19 (17)	5 (31)	14 (15)	--
Male	90(83)	11 (69)	79 (85)	--
Comorbidities ≥1	78 (72)	14 (88)	64 (69)	0.13
Diabetes	46 (42)	10 (63)	36 (39)	0.08
Hypertension	61 (56)	12 (75)	49 (53)	0.1
Ischaemic heart disease	17 (16)	3 (19)	14 (15)	0.7
Hypercholestrolaemia	40 (37)	9 (56)	31 (33)	0.08
Obesity (BMI >=30Kg/m2)	25 (23)	5 (31)	20 (22)	0.39
Obstructive sleep apnoea	6 (6)	2 (13)	4 (4)	0.18
Chronic heart failure	4 (4)	2 (33)	2 (2)	0.03
Chronic kidney disease	22 (20)	7 (44)	15 (16)	0.004
eGFR 60-89	17 (16)	5 (31)	12 (13)	--
eGFR 45-59	3 (3)	1 (6)	2 (2)	--
eGFR 30-44	1 (1)	1 (6)	0 (0)	--
eGFR <15	1 (1)	0 (0)	1 (1)	--
Active cancer	1 (1)	0 (0)	1 (1)	0.68

Abbreviations: COVID 19, Corona Virus Disease 2019 caused by SARS-CoV-2; ICU, intensive care unit; NOAF, new onset atrial fibrillation; IQR, interquartile range; eGFR, estimated glomerular filtration rate.
Data are presented as n (%), or n/N (%) unless specified. P values indicate difference between patients with NOAF and those without NOAF in ICU. P<0.05 was considered statistically significant.

Table 2: Clinical, laboratory and outcome findings of patients treated in ICU with COVID-19

	Normal range	Total (N=109)	With NOAF during ICU stay (n=16)	Without NOAF during ICU stay (n= 93)	P value
Clinical findings during ITU admission with COVID-19					
Acute kidney injury (AKI)		70 (64)	15 (94)	55 (59)	0.028
AKI not requiring RRT		31 (28)	7 (44)	24 (26)	--
Severe AKI requiring RRT		39 (36)	8(50)	31 (33)	--
Echocardiography findings*					
LV systolic function, median, (IQR), %	>55	60 (55-65)	60 (55-60)	60 (55-65)	0.36
Good LV systolic function ≥ 55%		83 (92)	15 (94)	68 (92)	--
Mild LVSD with EF 45-54%		2 (2)	0 (0)	2 (2)	--
Moderate LVSD with EF 36-44%		5 (5)	1 (6)	4 (5)	--
Severe LVSD with EF <=35%		1 (1)	0 (0)	1 (1)	--
Left atrial size					0.1
Normal		60 (67)	7 (44)	53 (71)	--
Mildly enlarged		27 (30)	8 (50)	19 (26)	--
Moderately enlarged		3 (3)	1 (6)	2 (2)	--
Laboratory findings during ITU admission with CoVID-19 -Median, (IQR)					
White blood cell count x10^9/ L	4.0-10.0	18 (14.0-25.5)	18 (13-30)	18 (14-24)	0.73
C-Reactive Protein mg/L	<3.0	333 (256-388)	324 (248-400)	333 (256-388)	0.8
Ferritin ug/L	41-400	1870 (1078-2904)	1670 (1128-2329)	1926 (1031-3018)	0.45
Creatinine Kinase unit/L	40-320	608 (279-1677)	1460 (350-2325)	583 (272-1593)	0.2
Troponin T ng/L	<14	80 (35-160)	83 (53-158)	80 (33-160)	0.5
D Dimer mg/L	0-0.5	17 (6-59)	18 (8-46)	17 (6-60)	0.9
Complications and outcome					
ECMO support		12 (11)	2 (13)	10 (11)	0.83
Venous thromboembolism		21 (19)	4 (25)	17 (18)	0.54
Arterial embolism		3 (3)	1 (6)	2 (2)	0.36
Therapeutic Anticoagulation					0.8
New onset AF		2 (2)	2 (12.5)	0 (0)	--
Venous/arterial thromboembolism		24 (22)	5 (31)	19 (20)	--
Hypercoagulable state **		7 (6)	0 (0)	7 (8)	--
Length of stay in ICU median,(IQR), d					
Survivors		35 (22-42)	42 (37-44)	32 (21-40)	0.03
Non survivors		17 (12-22)	18 (12-26)	15 (12-21)	0.39
In hospital death		38 (35)	11 (69)	27 (29)	0.002

Abbreviations: COVID 19,Corona Virus Disease 2019 caused by SARS-CoV-2; ICU, intensive care unit; NOAF, new onset atrial fibrillation; IQR, interquartile range; AKI, acute kidney injury; RRT, renal replacement therapy; LV, left ventricle; LVSD, left ventricular systolic dysfunction; ECMO, ;d, days.

Data are presented as n (%), or n/N (%) unless specified as median (IQR). P values indicate difference between patients with NOAF and those without NOAF in ICU. P<0.05 was considered statistically significant.

*Echocardiography was only performed in 90 patients (16 NOAF group and 74 without NOAF group) and the percentage is expressed accordingly.

** Therapeutic anticoagulation commenced in some patients with high thrombotic risk based on clinical assessment and with extremely elevated D-Dimer levels in the context of COVID-19 (7 patients).

course of illness and cardiac troponin T was raised in 91% of the study group above the 99th percentile upper reference limit (URL). Never the less, median left ventricular systolic function on echocardiography was with in normal range (60%; IQR 55-65)(Table 2). Echocardiography was performed based on clinical grounds in patients (83%) with suspected acute cardiac injury evidenced by serial troponin rise, electrocardiographic changes, arrhythmia or haemodynamic instability/ shock. Deterioration in left ventricular systolic function from baseline was observed only in three patients of which two admitted following acute myocardial infarction (AMI) and one developed AMI during COVID-19 illness due to an acute thrombus evident on coronary angiogram.

Eleven percent of our study population required ECMO for severe respiratory failure. Locally adopted guidelines were followed for management of venous thromboprophylaxis in COVID-19 and a modified anticoagulation regime with increased dose was advocated for patients with D-Dimer more than 3mg/L (normal range 0-0.5 mg/L). However, a small proportion of our study group (7 patients; 6%) received therapeutic dose of anticoagulation assessed by their thrombosis riske specially when the D-Dimer levels were extremely high (>80 mg/L).Sixty five percent of patients had D-Dimer levels 10 fold above the upper limits of normal (median 17 mg/L; IQR 6-59).Venous and arterial thromboembolism was one of the commonly observed complications[24 patients (22%)] with 76% diagnosed with pulmonary embolism on CTPA. Seven patients (44%) received therapeutic anticoagulation amongst NOAF group for AF, venous and arterial embolism and unusually elevated level of d-dimer. Majority among NOAF group had CHA_2DS_2VASc score ≥ 2 (15 patients; 7 patients scoring 3 and 2 patients scoring 4). As most of our study population had multi-organ involvement due to severity of the COVID illness, the decision for therapeutic dose of anticoagulation was made based on physician discretion as many (9 patients) were deemed high risk of bleeding. One-third of patients (33%) did not survive the illness and the median time from admission to ICU discharge was 35 days (IQR 22-42) (Table 2).

Clinical characteristics between patients with and without new onset atrial fibrillation

Patients who developed NOAF (n=16) during their ICU stay in comparison to non AF counterpart (n=93), were significantly older (median 65 year [IQR 59-71] vs 58 years [IQR 51-64]; p =0.001) and were high likely to have underlying chronic heart failure (2 [33%] vs 2[2%]; p=0.03) and chronic kidney disease (7 [44%] vs 15[16%]; p=0.004). Other comorbidities did not show any statistical significance between these two groups (Table 1). AKI has been more prevalent amongst the NOAF (94 % vs 59%; p=0.028) and nearly half of them required renal replacement therapy during ICU admission. Left atrium was enlarged above the normal limits in more than half of NOAF group (56% NOAF vs 28 % without NOAF; p= 0.032). Length of stay in ICU was significantly longer amongst survivors with NOAF than

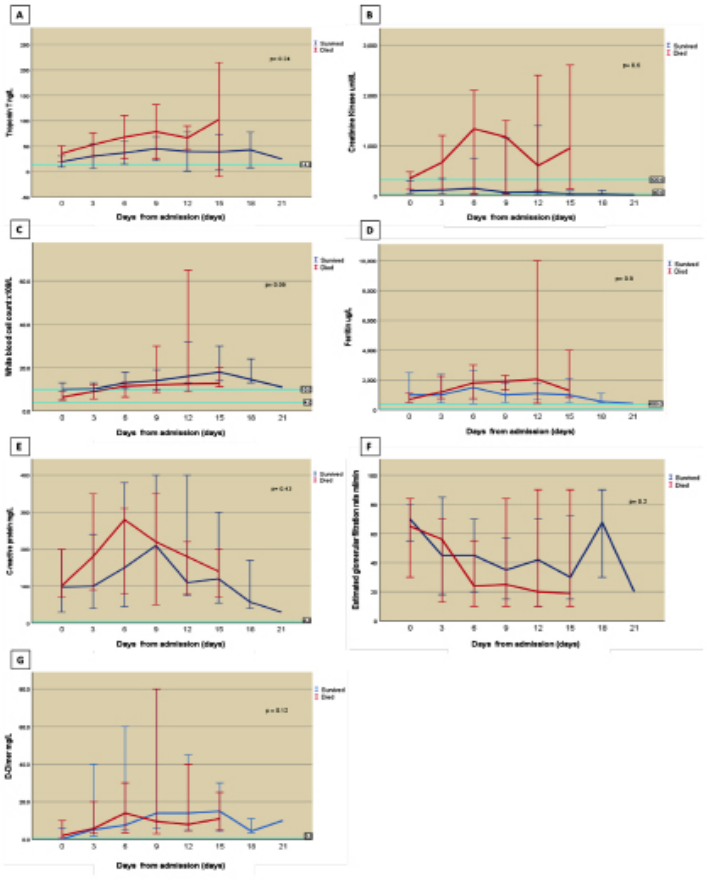

Figure 2: Temporal pattern of laboratory parameters illustrating the trend between survivors (7 patients) and non survivors (9 patients) from admission till onset of NOAF

A, Troponin; B, Creatinine kinase; C, White blood cell count; D, Ferritin; E, C-reactive protein; F , Estimated glomerular filtration rate; G, D-Dimer. Light blue solid line refers to the reference values for the blood markers where appropriate.

who remained in sinus rhythm (42 days [IQR 37-44 days] vs 32 days [IQR 21-40 days]; p=0.03) (Table 2). Survival outcome between both groups are illustrated in Figure 1. Increased in-hospital mortality was associated with presence of NOAF (OR 5.4; 95% CI 1.7-17; p=0.004) on univariate analysis and also when adjusting for covariates such as age, gender and comorbidities (p=0.042). One patient amongst the NOAF group died following an ischaemic stroke.

Survivors and non survivors of new onset atrial fibrillation

Temporal pattern of daily laboratory blood markers amongst patient who developed NOAF revealed raised median values for C-reactive protein, Ferritin, Creatinine kinase and troponin in non survivors than the survivors. However, the difference did not reach statistical significance probably because of the size of the group (Figure 1).Electrical cardioversion was performed in 2 of the 16 patients with NOAF due to haemodynamic instability with rapidly conducted AF and all patients received antiarrhythmic (amiodarone) and rate control drug therapy (bisoprolol, non dihydropyridine calcium channel blockers or/and digoxin) in the absence of contraindications. Restoration of sinus rhythm was achieved in 87% prior discharge or death (14 patients). One patient remained in persistent AF on discharge.

Incidence of NOAF was observed earlier during the course of illness among non-survivors (7 days;IQR 6.5-11.0 days vs 17days; IQR 11.0-23days) in comparison to patients who survived the illness (p<0.005).

Discussion

To our knowledge this is the first study demonstrating the incidence and outcome of new onset atrial fibrillation in patients with severe COVID-19 treated in ICU. There is increased evidence that the systemic inflammatory response per se is a predominant trigger of NOAF in critically ill patients [13]. In the literatures available on cardiovascular complications related to critically ill patients with COVID-19, the nature and classification of the arrhythmogenic events and their mechanisms have not yet well described. Our retrospective multicentre study assessing NOAF, showed an incidence of 14.6% amongst patients with COVID-19 treated in ICU and this is comparatively lower than the occurrence of NOAF reported in studies relating to severe sepsis in ICU in general [9-11]. This raises the question of whether the mechanism triggering AF in COVID-19 differ from other forms of sepsis despite high systemic inflammatory milieu by pro-inflammatory cytokine storm and possible direct viral invasion into cardiomyocytes through angiotensin-converting enzyme 2 (ACE2) receptors [15].

A systematic review by Kuipers et al, described that advanced age, male gender, obesity, organ failure were associated with development of AF during sepsis. In contrast to reported associations in the general population, diabetes and hypertension were not identified as risk factors in sepsis [16,17]. In our study advanced age, chronic heart failure and chronic kidney disease have shown to be a risk factor for development of NOAF among severely ill patients with COVID-19. Presence of diabetes, obesity or hypertension has not been identified as trigger for NOAF in our cohort (Table 1).

Patients with and without NOAF did not have any significant difference in the trend of inflammatory markers or troponin, however AKI was a risk for NOAF in patient with severe form of COVID-19 infection.

Just over 90% of our study population showed raised troponin T level above the normal range, but there was no significant association with NOAF or indeed left ventricular systolic function.Further detailed studies with cardiac MRI may help to assess the degree of myocardial involvement through tissue characteristics. There is compelling evidence that LA size is an independent predictor for atrial fibrillation in general population [18-20] and likewise in our cohort with severe COVID-19, enlarged LA size certainly remained a risk factor for NOAF.

Uncontrolled activation of coagulation cascade following lung injury contributes to lung inflammation in ARDS [21]. In general, significantly higher D-Dimer levels are found in patients with severe pneumonia/ARDS and also shown to be a predictor of poor clinical outcome and mortality [22]. COVID-19 data from recent studies described similar findings [14, 23] and our data reveal very high levels of D-Dimer in our cohort with more than one-third having levels >50mg/L. This indicates the severity of COVID-19 infection and the thrombosis risk in our study population, however did not achieve statistical significance when considering the in-hospital death.

The manifestation of even a single episode of AF is associated with increased mortality and poor outcome in critically ill patients with sepsis [10,11,16]. In this study the occurrence of NOAF was strongly associated with poor outcome. Patients who develop NOAF earlier during the course of COVID-19 illness had worse outcome and this may be a useful marker for physicians to predict prognosis.

Patients with severe sepsis who developed NOAF have a greater risk of in-hospital stroke than patients with pre-existing AF or individuals without history of AF [15,24]. We have reported one case of ischaemic stroke amongst the group developed NOAF with poor outcome has risk of arterial thromboembolism due to hypercoagulable state.

Anticoagulation significantly reduces the risk of stroke amongst patients with high risk factors, based on CHA_2DS_2VASc score (congestive heart failure, hypertension, age, diabetes mellitus, stroke, vascular disease and sex). However there is not much evidence to support anticoagulating critically ill patients in ICU which may expose them to risk of bleeding during sepsis [25,26] or invasive intensive care management. Virally driven hyper-inflammation with cytokine release will lead to hypercoagulable state and propensity for disseminated intravascular coagulation (DIC) in severe COVID-19 [27]. This is increasingly evident as substantial proportion of patients develop venous and arterial thromboembolic complications which was seen in our cohort. This may in turn could increase the risk of stroke in patients who develop NOAF with severe COVID-19, and careful assessment regarding decision on anticoagulation is warranted in these patients irrespective of CHA_2DS_2VASc score. However, further studies are needed to determine the value of anticoagulation in treating NOAF in severe COVID-19 patients.

Limitations

We have only included 109 patients from the height of first wave confirmed with COVID-19 treated in ICU and a larger ICU cohort is required to verify our conclusions. The key strength of our study is

that we only included patients with significantly high inflammatory burden due to severe COVID-19 as evidence by almost all patients requiring mechanical ventilation for severe ARDS. We had incomplete data on echocardiography as they were performed if suspected acute cardiac injury or arrhythmia during ICU stay. Our study does not include patients with existing AF and to patients in non-ICU setting with COVID-19.

Conclusion

Incidence of new onset atrial fibrillation was not high in patients with severe COVID-19 regardless of inflammatory burden. Nevertheless higher in-hospital mortality was demonstrated in patients with NOAF, especially when observed earlier during the course of illness. Despite understanding the hypercoagulable milieu of the disease, the benefit of anticoagulation for prevention of stroke during the acute stage severe COVID-19 remains unclear. Further larger studies are warranted to assess the incidence of stroke associated with NOAF in severe COVID-19 infection.

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UBLED AF (Uninterrupted BLackpool EDoxaban vs Warfarin vs Rivaroxaban in Atrial Fibrillation/Flutter ablation) Study

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Abstract

Aim: Catheter ablation in patients with atrial fibrillation (AF)/atrial flutter carries a risk of thromboembolism and major bleeding. In light of recent prospective trial data on the safety and efficacy of uninterrupted edoxaban in patients undergoing AF/flutter ablation, real-world Data was aimed for validation.

Methods: A total of 228 patients who underwent AF/atrial flutter ablation over 14 months at our centre were retrospectively analyzed. All patients received uninterrupted oral anticoagulation for at least 4 weeks prior to ablation and 3 months post-ablation. Both bleeding and thromboembolic events were assessed at 24 hours comparing patients on warfarin, rivaroxaban and edoxaban.

Results: Mean age of patients were 68.5 +/- 8 years in the warfarin group (N =86), 63.4 +/- 10.6 years; in the edoxaban group (N =63) and 62.3 +/- 11.6 years in the rivaroxaban group (N =79). CHADSVASc scores were 2.43 +/- 1.34, 1.68 +/- 1.34 and 1.64 +/- 1.38 respectively. The mean left atrial sizes were 42.7 +/- 6.8 mm, 42.0 +/- 6 mm and 41.1 +/- 6.5 mm respectively. The study endpoint was death, acute thromboembolism or major bleeding. There was 1 pericardial effusion (1.2%) in the warfarin group, 1 pericardial effusion and 1 transient ischaemic attack (2.5%) in the rivaroxaban group and 1 pericardial effusion needing drainage (1.6%) in the edoxaban group. There were no significant differences in the study endpoints between groups.

Conclusion: This real-world study demonstrated no significant difference in safety and efficacy between uninterrupted edoxaban, warfarin and rivaroxaban in patients undergoing AF/flutter ablation.

Introduction

AF ablation is technically challenging and is associated with peri-procedural risks including thromboembolicevents (<1%), bleeding complications related to tamponade (1-2%) and vascular complications (2-4%).The increased risk of thromboembolic complications is likely related to the exacerbation of the baseline pro-thrombotic state by catheters in the left atrium (LA), endothelial denudation, char formation and tissue inflammation from ablation in the LA. Minimizing these complications with optimal peri-procedural anticoagulation with an appropriate balance between bleeding and thrombosis is critical to the safety of the procedure. Optimal peri-procedural anticoagulation protocols to minimize these complications are still largely debated and are non-uniform.[1,11,12]

Key Words

Catheter Ablation; Atrial Fibrillation; Edoxaban; Complications; Anticoagulation.

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Studies have started focusing on the use of direct oral anticoagulants (DOACs) in the peri-procedural period and compared them to warfarin in terms of bleeding and thromboembolic complications. In a meta-analysis of 70 studies with 4962 patients, it was concluded that DOACs were both safe and effective when used in an uninterrupted fashion in patients undergoing AF ablation [2-4].The incidence of cerebral thromboembolic events was low with these agents and not significantly different from uninterrupted VKAs, whereas major bleeding was significantly reduced with DOACs.[2,9,10]

There is still shortage of real world clinical data have evaluating the uninterrupted rivaroxaban and apixaban individually in patients undergoing AF ablation[3–5]. Recently, ELIMINATE - AF study compared the safety and efficacy of edoxaban with warfarin in patients undergoing AF ablation with endpoints of death, stroke or major bleeding.

Complimenting this data, UBLED AF study aimed to evaluate real-world data observed from our own centre on the safety and efficacy of

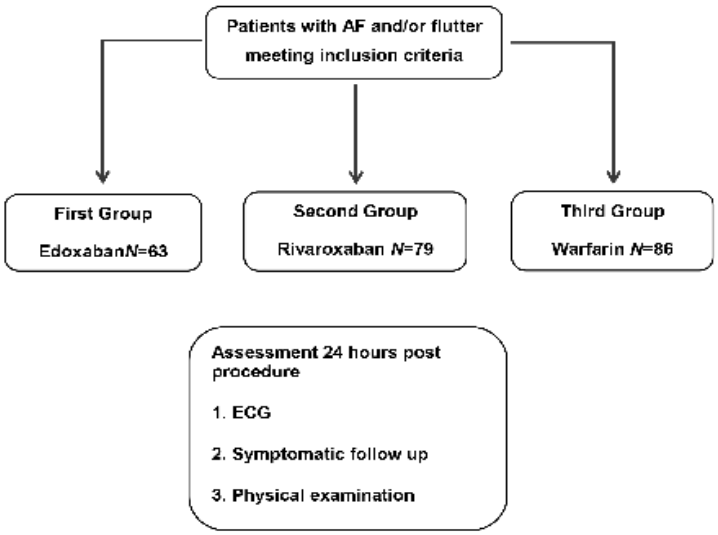

Figure 1: Study Method and Follow-up Flow Chart

Patients on uninterrupted anticoagulation 4 weeks prior to and 3 months post AF/flutter ablation with edoxaban were compared with those on rivaroxaban and warfarin. Records of assessment at 24 hours post-procedure were used to evaluate the occurrence of complications.

uninterrupted edoxaban in the peri-procedural period in cases of AF and atrial flutter ablation compared towarfarin and rivaroxaban.

Methods

A total of 228 patients who underwent AF and atrial flutter ablation on uninterrupted anticoagulation using edoxaban, rivaroxaban and warfarin over 14 months were reviewed retrospectively in this observational study. Patients on twice a day dosageof dabigatran and apixaban were excluded because our local practice was to interrupt anticoagulation on the day of the procedure with these DOACs.

The first group consisted of all patients on edoxaban,the second group all patients on rivaroxaban and third group those on warfarin during their ablation. All anticoagulation was uninterrupted for at least 4 weeks prior to ablation and 3 months post-ablation. For patients on warfarin, INRs were maintained above 2 for at least 4 weeks before the procedure. Baseline evaluation included a transthoracic echocardiogram, blood tests and a 12 lead ECG (Figure 1).

Patients were instructed to take their medication in the evening prior to the procedure. All patients were hence on uninterrupted anticoagulation on the day of the procedure. It was resumed 4-6 hours after haemostasis following ablation.

Transoesophageal echocardiography was performed if indicated to rule out LA appendage thrombus and to guide trans-septal puncture during the procedure. During the ablation procedure, a bolus of 100 IU/kg body weight of unfractionated heparin was given around the time of trans-septal puncture. The activated clotting time (ACT) was maintainedbetween 300 to 400 s while catheters remained in the LA. The technique of the procedure was at the discretion of the operator but remained similar between the 3 operators involved.

Bleeding events were defined as anybleeding requiring blood transfusion, haematomas requiring surgical intervention, and pericardial effusions. Cerebrovascular accidents and transient ischaemic attacks were considered asthromboembolic complications after ruling out intracranial haemorrhage.

The documentation of thereassessment of patients at 24 hours post AF and atrial flutter ablation was reviewed carefully which was part of standard care and which recorded any adverse events up until that time.

Formal ethical approval was not required due to the local, retrospective and observational nature of the study. however, appropriate protection of patient information and data was ensured.

Statistical Analysis

Data between the warfarin, rivaroxaban and edoxaban groups were analysed using multivariate analysis with age and gender as covariates. Warfarin and rivaroxaban were used as references, respectively. Statistical analyses were descriptive. All continuous variables were expressed in terms of mean and standard deviation. Categorical data were expressed as numbers and proportions. Probability values of <0.05 were considered to be statistically significant. All analysis was performed using SPSS software.

Results

Table 1: Patient Characteristics

Patient Characteristics	Warfarin N=86	EdoxabanN=63	Rivaroxaban N=79
Age (years)	68.5 +/- 8.0	63.4 +/- 10.6	62.3 +/- 11.6
Gender, n (%)			
Male	52 (60.5)	45 (71.4)	56 (70.9)
Female	34 (39.5)	18 (28.6)	23 (29.1)
Medical History, n (%)			
HTN	40 (46.5)	24 (38.1)	24 (30.4)
DM	8 (9.3)	6 (9.5)	4 (5.1)
CVA/TIA	4 (4.7)	2 (3.2)	5 (6.3)
CAD/PVD	16 (18.6)	9 (14.3)	12 (15.2)
CHF	15 (17.4)	8 (12.7)	11 (13.9)
CHADSVASc	2.43 +/- 1.34	1.68 +/- 1.34	1.64 +/- 1.38
Baseline ECG, n (%)			
SR	36 (41.9)	31 (49.2)	45 (57.0)
AF/AT	50 (58.1)	32 (50.8)	34 (43.0)
LA diameter (mm)	42.7 +/- 6.8	42.0 +/- 6.0	41.1 +/- 6.5
Antiplatelet Drugs, n (%)			
Aspirin	3 (3.5)	4 (6.3)	4 (5.1)
Clopidogrel	4 (4.7)	1 (1.6)	2 (2.5)
Ticagrelor	1 (1.2)	0	0
Antiarrhythmic Type Drugs, n (%)			
Flecainide	11 (12.8)	7 (1.1)	14 (17.7)
Sotalol	7 (8.1)	2 (3.2)	2 (2.5)
Dronedarone	5 (5.8)	0	1 (1.3)
Amiodarone	9 (10.5)	1 (1.6)	6 (7.6)
Rate Limiting Drugs, n (%)			
Beta-blockers	70 (81.4)	44 (69.9)	60 (76.0)
Ca2+-channel blockers	12 (14.0)	6 (9.5)	6 (7.6)
Digoxin	17 (19.8)	9 (14.3)	7 (8.9)

Continuous variables reported as a mean +/- standard deviation (SD) and categorical data as numbers and proportions.

Table 2: Procedure Characteristics

Procedure Characteristics	Warfarin N=86	EdoxabanN=63	Rivaroxaban N=79
AF Ablation Only, n (%)	70 (81.4)	42 (66.7)	53 (67.1)
Flutter Ablation Only, n (%)	13 (15.1)	18 (28.6)	17 (21.5)
Combination AF/Flutter, n (%)	3 (3.5)	3 (4.8)	9 (11.4)
AF type, n (%)			
Paroxysmal	27 (31.4)	21 (33.3)	35 (44.3)
Persistent	46 (53.5)	24 (38.1)	27 (34.2)
Type of Anaesthesia, n (%)			
Local	46 (53.5)	36 (57.1)	48 (60.8)
General	40 (46.5)	27 (42.9)	31 (39.2)
Ablation Energy Used, n (%)			
Laser	13 (15.1)	18 (28.6)	21 (26.6)
Cryoablation	4 (4.7)	9 (14.3)	2 (2.5)
RF*	69 (80.2)	36 (57.1)	56 (70.9)
Type of Procedure, n (%)			
De novo	53 (61.6)	46 (73.0)	70 (88.6)
Redo	33 (38.4)	17 (27.0)	9 (11.4)
INR (if applicable), n (%)			
Less than 2	2 (2.3)	N/A	N/A
2-3	81 (94.2)	N/A	N/A
More than 3	3 (3.5)	N/A	N/A
Closure, n (%)			
Manual only	6 (7.0)	4 (6.3)	3 (3.8)
Z-suture only	5 (5.8)	12 (19.0)	4 (5.1)
Femstop only	71 (82.6)	44 (69.8)	71 (89.9)
Combination	4 (4.7)	3 (4.8)	1 (1.3)
Fluoroscopy Dose (MGy)	71.8	49.7	57.4
Fluoroscopy Time (min)	16.5 +/- 10.6	14.8 +/- 9.2	14.8 +/- 10.4

Continuous variables reported as a mean+/-standard deviation (SD) and categorical data as numbers and proportions, *RF = radiofrequency.

A total of 228 adult patients with non-valvular AF/atrial flutter who underwent elective catheter ablation over 14 months were studied. Baseline patient characteristics were similar (Table1). The warfarin group (N=86) included 52 males and 34 females with a mean age of 68.5 +/-8 years and a mean CHADSVASc score of 2.43 +/- 1.34. The edoxaban group (N=63) included 45 males and 18 females with a mean age of 63.4 +/- 10.6 years and a mean CHADSVASc score of 1.68 +/- 1.34. The rivaroxaban group (N=79) included 56 males and 23 females with a mean age of 62.3 +/- 11.6 years and a mean CHADSVASc score of 1.64 +/- 1.38. The mean LA sizes were 42.7+/-6.8 mm, 42.0+/-6 mm and 41.1 +/-6.5 mm respectively (P=0.473). Proportions of comorbidities, baseline ECG rhythm and medications are shown in table 1.

Procedural characteristics were also similar (Table 2). The proportion of patients who underwent AF ablation only in the warfarin group was 81.4%, in the edoxaban group 66.7% and in the rivaroxaban group 67.1%. The proportion of patients who underwent atrial flutter ablation only in the warfarin group was 15.1%, in the edoxaban group 28.6% and in the rivaroxaban group 21.5%. The remaining patients underwent both AF and atrial flutter ablations during the same procedure. Other features compared in table 2 are AF type, anaesthesia type, ablation energy type, de novo versus redo procedure, INR level (for warfarin only), closure method, fluoroscopy dose and fluoroscopy time. There was a single case of TIA noticed in patient on uninterrupted Rivaroxaban. On an overall basis, as per table 3, 2 patients on rivaroxaban had minor acute bleeding complications (HR (95% CI); P value rivaroxaban vs warfarin 1.09 (0.07 – 17.45); 0.95 HR (95% CI) and P value rivaroxaban vs edoxaban 0.80 (0.05 – 12.98); 0.87). There was single case of pericardial effusion (1.2%) in the warfarin group. However,1 pericardial effusion and 1 transient ischaemic attack (2.5%) were observed in the rivaroxaban group and 1 pericardial effusion needing drainage (1.6%) in the edoxaban group. There were no significant differences in the study endpoints between groups.

Endpoints

There were no deaths in any group in this study. There was 1 bleeding event in each of the three groups in the form of pericardial effusions, resolving spontaneously except in the case of edoxaban where drainage was required. There was 1 thromboembolic event in the rivaroxaban group which was a transient ischaemic attack. The total event rate was therefore 1.2% in the warfarin group, 2.5% in the rivaroxaban group and 1.6% in the edoxaban group, with P values of 0.83 comparing edoxaban to warfarin, 0.51 comparing rivaroxaban to warfarin and 0.70 comparing rivaroxaban to edoxaban (Table 3).

Discussion

During the last decade, several new oral anticoagulants have been approved for clinical use including apixaban and edoxaban. NOACs have made their way into the guidelines for non-valvular AF due to multiple advantages compared to warfarin; e.g., chances for drug-to-drug interaction, the variation in dosage to response, and a narrow therapeutic window, to name a few.

There is lack of clinical studies which have compared traditional uninterrupted warfarin to all the new oral anticoagulants for patients who are undergoing atrial fibrillation or atrial flutter ablation. The current ACC/AHA/EHRA/APHRS guidelines support use of new oral anticoagulants compared to warfarin. All 3 operators at our centre used similar techniques for anticoagulation, trans-septal puncture and performing ablation in this study. Protocol for anticoagulation during the procedure with IV heparin was also standard within the department, using 100 IU/kg around the time of trans-septal puncture and maintaining an ACT target >300 seconds.

These data were collected several years ago, and the local practice was to continue the same anticoagulant for a patient already on warfarin. However, our practice has changed over the last few years where most patients get started in DOAC as per national and international guidelines. We compared uninterrupted edoxaban to VKAs and rivaroxaban in patients with atrial fibrillation or atrial flutter underdoing ablation procedure. No significant difference was found in acute complications including bleeding and thromboembolic events between all 3 groups (a total of 4 across all groups, including 1 pericardial effusion in each group and 1 transient ischaemic attack in the rivaroxaban group). In our observational study, the event rate for complications was very low across all groups. At local Institute, reversal agents are given for any cases that needed pericardiocentesis. The anticoagulation is immediately restarted once patient is stable and confirmed by a cardiac echo. The remaining cases were managed

conservatively without reversal. Anticoagulation was recommenced within 24 hours after confirmation with serial echo.

Randomised control trials have been conducted to assess the safety of uninterrupted rivaroxaban (VENTURE-AF)[4], dabigatran (RE-CIRCUIT)[3], apixaban (AXAFA-AFNET 5)[5] and most recently edoxaban (ELIMINATE-AF) peri-procedurally.[6]

VENTURE-AF was the first randomised trial to compare rivaroxaban to VKAs in an uninterrupted fashion for peri-procedural anticoagulation in patients with non-valvular AF. It showed that the incidence of major bleeding was low (0.4%; 1 major bleeding event). Similarly, thromboembolic events were low (0.8%; 1 ischemic stroke and 1 vascular death). All events occurred in the VKA arm and all after catheter ablation. The study concluded that in patients undergoing catheter ablation for AF, the use of uninterrupted rivaroxaban was feasible and event rates were similar to those for uninterrupted VKA therapy.[4] Similarly, in the randomised trial RE-CIRCUIT comparing dabigatran to VKAs, the incidence of major bleeding events during and up to 8 weeks after ablation was lower with dabigatran than with warfarin (5 patients [1.6%] vs. 22 patients [6.9%], P=0.001). Dabigatran was associated with fewer peri-procedural pericardial tamponades and groin haematomas than warfarin. The two treatment groups had a similar incidence of minor bleeding events. One thromboembolic event occurred in the warfarin group.[3]

In the randomised AXAFA-AFNET 5 trial, uninterrupted apixaban was compared to uninterrupted warfarin. The primary outcome was a composite of death, stroke ormajor bleeding, which were observed in 22 of 318 patients on apixaban and 23 of 315 patients on warfarin (non-inferiority P=0.0002). There was 1 death in each group and 2 strokes in the apixaban group. There were 2 tamponades managed with drainage in the apixaban group compared to 5 in the warfarin group. The study concluded that apixaban was non-inferior to warfarin in terms of safety and efficacy when used without interruption peri-procedurally.[5]

The ELIMINATE-AF trial was a prospective randomised study which was conducted to assess the safety and efficacy of once-daily edoxaban 60 mg (30 mg in patients indicated for dose reduction) vs VKAs in non-valvular AF patients undergoing catheter ablation. In this study, a total of 614 patients were randomised to edoxaban or VKAs (at a 2:1 ratio) to obtain 417 patients fully compliant with the protocol. The primary efficacy endpoint was a composite of all-cause death, stroke and major bleeding with a primary safety endpoint of major bleeding.[6] The primary endpoint in the 'per-protocol population was observed in 1.3% of edoxaban (N=4) and 3% of VKA patients (N=3) between the start of ablation and the end of treatment. In the intention-to-treat population, which included patients who received at least one dose of the study drug but did not necessarily undergo ablation, the primary endpoint was seen in 2.5% of edoxaban (N=10) and 1.5% of VKA patients (N=3). Pericardial tamponade occurred in 3 patients on edoxaban and 2 patients on VKA. Puncture site bleeding occurred in 3 edoxaban patients and 1 VKA patient. There were 2 intracranial bleeds and 1 gastrointestinal bleed in the edoxaban group. There was 1 ischaemic and 1 haemorrhagic stroke, both in patients on edoxaban. Small cerebral micro-emboli were detected in 13.8% (16 patients) of those who received edoxaban and 9.6% (5 patients) of those in the VKA group (P=0.62). The overall hazard ratio was 1.68 (confidence interval 0.46 - 6.47). The study concluded that uninterrupted edoxaban therapy represented a valid alternative to uninterrupted VKA treatment in patients undergoing AF ablation.[6]

In a 2017 meta-analysis of databases comparing DOACs to warfarin in patients undergoing AF ablation, the risk of clinical thromboembolic events was exceedingly low and not significantly different between groups and it also showed that silent cerebral events could occur in 1 in 10 patients despite uninterrupted anticoagulation.[2,7,8] In terms of major bleeding, it was halved with uninterrupted DOACs compared with uninterrupted VKAs and this difference was persistent in a subgroup analysis of randomised and cohort studies with matched controls.

Our real-world data, therefore, supports the randomised trials, namely both ELIMINATE-AF and VENTURE-AF trials, to suggest that edoxaban is similar in safety and efficacy to warfarin and rivaroxaban when used peri-procedurally during AF / atrial flutter ablation.

Study Limitations

This was an observational study subject to confounding and selection bias. The event rate was low and therefore subject to error. This was a single-centre study; however, a strength is that all 3 operators had similar techniques for anticoagulation, trans-septal puncture and performing ablation. A complete dataset for the ACT measured during each procedure was not available; however, standard practice was similar in all cases with IV heparin given at 100 IU\kg maintaining an ACT target >300 seconds. Patients on dabigatran and apixaban were excluded since they are both administered twice daily and local practice at this hospital is to omit the morning dose of these DOACs on the day of the procedure; thus, we were not using them in an uninterrupted fashion.

Conclusion

In this single-centre observational study, there was an overall low number of acute bleeding and thromboembolic complications with no significant difference among all 3 groups. This real-world study further suggests that edoxaban carries a similar safety and efficacy profile

Table 3: Acute Complications

Acute Complication	Warfarin N=86	Edoxaban N=63	Rivaroxaban N=79	HR (95% CI); P value warfarin vs edoxaban	HR (95% CI); P value rivaroxaban vs warfarin	HR (95% CI); P value rivaroxaban vs edoxaban
Total, n (%)	1 (1.2)	1 (1.6)	2 (2.5)	0.73 (0.04 – 12.11); 0.83	2.18 (0.23 – 20.97); 0.51	1.59 (0.16 – 15.56); 0.70
CVA/TIA, n (%)	0	0	1 (1.3)	NS	0.30	0.37
Bleeding, n (%)	1 (1.2)	1 (1.6)	1 (1.3)	0.73 (0.04 – 12.11); 0.83	1.09 (0.07 – 17.45); 0.95	0.80 (0.05 – 12.98); 0.87

HR = hazard ratio, CI = confidence interval, NS = not significant

compared to warfarin and rivaroxaban when used in an uninterrupted fashion peri-procedurally for AF/ atrial flutter ablation.

Disclosures

Dr K Abozguia has received honoraria from Daiichi Sankyo, Bayer and Boehringer Ingelheim; Dr S Chalil has received honoraria from Daiichi Sankyo, Bayer, Boehringer Ingelheim and BMS/Pfizer; all other authors have no conflicts to declare.

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The Story of a Migrating Pericardial Drain and Perforation!

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Abstract

A patient underwent the LARIAT left atrial appendage (LAA) ligation procedurewith persistent atrial fibrillation history. The procedure was done successfully. A transthoracic echocardiography did not show pericardial effusion. The patient was examined under fluoroscopy where the tip of the drain was not in the pericardial space and contrast injection pericardial drain confirmed its location in the inferior vena cava.

Case Report

An 80-year-old woman with a history of persistent atrial fibrillation underwent the LARIAT left atrial appendage (LAA) ligation procedure. The procedure was uneventful and at the end a straight pericardial drain (Boston Scientific, Marlborough, MA, USA) was placed to allow further evacuation of the space from the ligated LAA. The patient did well for the first 18 hours with no further drainage. The next day morning patient complained of significant chest pain and many bouts of deep coughing. Immediately after that the patient's pericardial drain starting putting out a significant amount of dark venous blood suggestive of possible recurrent pericardial effusion. A transthoracic echocardiography did not reveal any pericardial fluid. The patient was examined under fluoroscopy where the tip of the drain was not clearly visible in the pericardial space. Contrast injection through pericardial drain confirmed its location in the hepatic vein-inferior vena cava (IVC) confluence. (Panel A, arrows). Computed tomography (CT) also was performed and identified that the pericardial drain has migrated into the IVC and the tip was in the middle hepatic vein (Panel B-C, arrows). This confirmed the migration of the pericardial drain tip from the pericardial space into the IVC. Further review of the echocardiography and CT confirmed a very thin area of tissue at the junction of the IVC and right atrium (RA). It is likely that this vulnerable area was punctured due to patient movement and violent bouts of coughing. The location of the drain was confirmed and repaired under direct visualization in the operating room transesophageal echocardiography TEE was performed and confirmed the catheter to be in the IVC, piercing it right at the atrial junction (Panel D, arrow). Median sternotomy was performed and established aortic and right atrial append age cannulation. It should be noted that the catheter was still in the right atrial and the IVC junction (Panel E, arrow). The catheter was pulled, and the hole was closed with a suture with no residual bleeding. A full maze procedure was also done. There was a LARIAT suture noted on the left atrial appendage that was excluding a large part of it (Panel F, arrow). The patient tolerated the procedure well, then she was discharged in stable condition.

It is important to realize vulnerable anatomy and make sure that the catheter tip doesn't migrate towards the great vessels. It is preferred to avoid a straight tipped pericardial drain and care must be taken to ensure the location of the tip away from the inferior or superior vena cava.

Key Words

Atrial Fibrillation, Radiofrequency Ablation, Natriuretic Peptides, Left Atrial Ejection Fraction, Left Atrial Strain.

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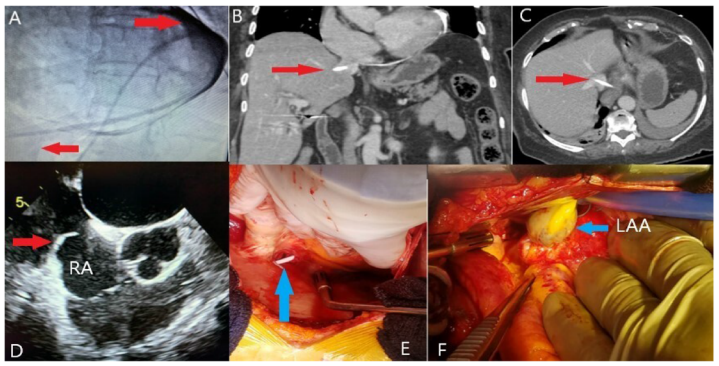

Figure 1: The distal part of catheter shows contrastin the vena cava inferior with Fluoroscopy (Figure-A, arrows) and the catheter was demonstrated with CT (Figure-B and C, arrows) and transesophageal Echocardiography (Figure-D, arrow) in the right atrium and inferior vena cava junction. Intraoperative images show the catheter (Figure-E, arrow) and excluded left atrial appendage (Figure-F, arrow)

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Biomarkers of Metabolic Syndrome: Role in Pathogenesis and Pathophysiology of Atrial Fibrillation

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Abstract

The relationship between Metabolic syndrome and Atrial Fibrillation is confirmed by many studies. The components of Metabolic syndrome cause remodeling of the atrial. Metabolic syndrome and metabolic derangements of the syndrome could be the cause of the pathogenesis of AF. This review article discusses the major biomarkers of Metabolic syndrome and their role in the pathogenesis of AF. The biomarkers are adiponectin, leptin, Leptin/ Adiponectin ratio, TNF-α, Interleukin-6, Interleukin-10, PTX3, ghrelin, uric acid, and OxLDL.The elevated plasma levels of adiponectin were linked to the presence of persistent AF. Leptin signaling contributes to angiotensin-II evoked AF and atrial fibrosis. Tumor necrosis factor-alpha involvement has been shown in the pathogenesis of chronic AF. Similarly, Valvular AF patients showed high levels of TNF-α. Increased left atrial size was associatedwith the interleukin-6 because it is a well-known risk factor for AF. Interleukin-10 as well as TNF-α were linked to AF recurrence after catheter ablation. PTX3 could be superior to other inflammatory markers that were reported to be elevated in AF. The serum ghrelin concentration in AF patients was reduced and significantly increased after treatment. Elevated levels of uric acid could be related to the burden of AF. Increased OxLDL was found in AF as compared to sinus rhythm control.

Introduction

Metabolic syndrome (MetS) is a collection of conditions such as hypertension, obesity, insulin resistance, and dyslipidemia. Also, defined as a cluster of metabolic risk factors and this clustering category of metabolic syndrome is known as syndrome X. Various terms are used to refer to the Metabolic Syndrome in individuals like insulin resistance syndrome, metabolic syndrome X, and Reaven's syndrome. The primary clinical outcomes of metabolic syndrome are cardiovascular diseases. The prevalence of metabolic syndrome increases as age is increasing and in the USA about 34% of adult populations have Metabolic Syndrome [1,2]. The defining criteria of metabolic syndrome, according to the National Cholesterol Education Program Adult Treatment Panel III guidelines,[3] explains in flowchart 1.

Atrial Fibrillation (AF) is a common kind of cardiac arrhythmia in which heartbeats rate excess from normal rate and is mostly found in the elderly population which has increased the rate of mortality, morbidity, and disability. The risk of stroke, heart attack, and death rates have increased due to AF [4-6]. Similarly, the pathogenesis of AF has been caused due to the numerous components of metabolic syndrome which affect AF triggers or the atrial substrate [7]. In the same way, the initiation and maintenance of AF are due to the atrial electrical, electrical remodeling (changes the ion channel function and calcium handling of the cells) and structural remodeling. Numerous components of metabolic syndrome cause remodeling of the atrial. Interstitial fibrosis with structural remodeling leads to heterogeneous electrical substrates with differences in conduction velocities which promotes AF[8,9].

Furthermore, Watanabe et al. study had concluded that an increased risk of AF was linked to metabolic syndrome and metabolic derangements of the syndrome that might be important for the pathogenesis of AF [10]. Similarly, Mechanical stress in the atrium might predispose the AF which was caused by metabolic syndrome whereas, electrophysiological remodeling, as well as structural remodeling, are criteria for atrial fibrillation to perpetuate [11-14]. Like wise, the structural substrate such as dilatation, fibrosis, atrial stretch, at gap junctions' disruption of cell coupling has occurred, and loss of muscle mass [11-

Key Words

Metabolic syndrome, Atrial Fibrillation, Adiponectin, Leptin, Tumor necrosis factor-alpha, Interleukin- 6, Interleukin -10, Ghrelin, Uric acid, OxLDL

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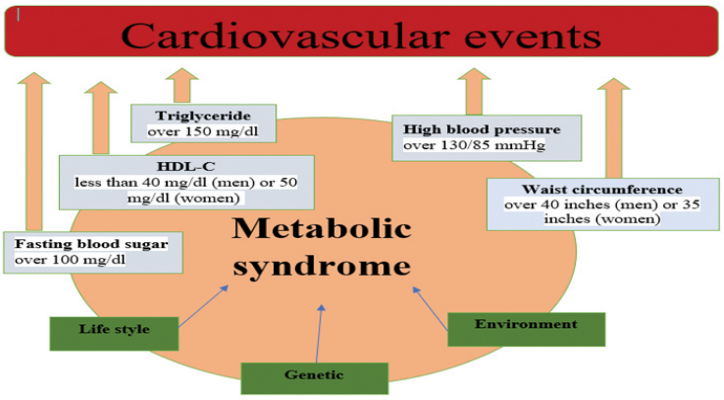

Flowchart 1: **Metabolic syndrome leads to cardiovascular diseases: The defining criteria of metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III guidelines[3].**

[13]. In the same way, the integral components of metabolic syndrome including obesity and hypertension might cause atrial dilatation and stretch which had been resulted in a structural substrate predisposing to AF [15,16].

Further, Nicolaou et al study had reported that enlargement of an atrium in patients with nonvalvular AF was linked to metabolic syndrome [17]. Also, structural remodeling might change the cellular electrophysiology which resulted in AF. During the episodes of atrial fibrillation, the rapid atrial rates could lead to further atrial remodeling, more frequent and severe episodes of atrial fibrillation a phenomenon recognized as "AF begets AF [18,19].

In addition, A biomarker or biological marker is a measurable indicator of some biological state or condition. It is used to evaluate or measure the normal biological process, pharmacologic response, and pathogenic processes to a therapeutic intervention. So, In MetS, many different biomarkers are used in the early detection and risk stratification in MetS patients and their role in cardiovascular diseases. It includes leptin, Interleukin-6, Tumor Necrosis Factor -Alpha, uric acid, Interleukin-10, ghrelin, adiponectin, paraoxonase, oxidized LDL, plasminogen Activator inhibitor – 1 [20,21].

In this review article, we provided an overview and focus on the basic role of different biomarkers of metabolic syndrome and mainly focus on pathophysiological aspects of different biomarkers of metabolic syndrome in Atrial Fibrillation. There are many biomarkers of metabolic syndrome. However, our review article focuses only on adiponectin, leptin, Leptin/ Adiponectin ratio, TNF-α, Interleukin-6, Interleukin-10, PTX3, ghrelin, uric acid, OxLDL,and their pathophysiological role in the development and progress of AF. In conclusion, we have provided a viewpoint on the recent pathophysiological role in AF.

Different databases including Google Scholar, PubMed, and Science direct were used to review the literature. The last date of the search was 10 July 2021. Many keywords were used for searching the literature such as metabolic syndrome, Atrial Fibrillation, interleukin- 6, interleukin -10, tumor necrosis factor-alpha, uric acid, leptin, adiponectin. The language of clinical studies was restricted to English. We did not limit the time frame although more recent studies were favoured.

Role of a major biomarker of Metabolic syndrome in AF

According to the literature, there are many biomarkers of metabolic syndrome. However, this review article has discussed only major biomarkers of metabolic syndrome such as adiponectin, leptin, leptin/ adiponectin ratio, TNF-α, interleukin-6, interleukin-10, Pentraxin-3, ghrelin, uric acid, and Oxidized Lipoprotein Lipase which played their pathophysiological role in atrial fibrillation as explained in table 1.

1. Adiponectin

Adiponectin is produced from adipocytes and its high-molecular-weight form play role in most potent metabolic activity and circulating levels are higher in females as compared to males due to the stimulating activity of testosterone on adiponectin secretion [21]. Moreover, an important role in metabolic balance and increases the risk of vascular, metabolic, and cardiac due to its low levels. Likewise, Maroniet al. study has reported decreased levels of adiponectin in metabolic syndrome patients [22]. Conversely, Matsuzawa et al. study also demonstrated the positive effect on metabolic protection mainly in the atherogenic process by potentially inhibitory activity [23]. On the contrary, Fu Y study et al. have conducted to show that metabolic syndrome components were inversely related to adiponectin levels and have beneficial effects on metabolic disorders [24].

Furthermore, Shimano et al. (2008) conducted a study that explained the atrial remodeling in atrial fibrillation occurred due to obesity-related conditions. Adiponectin has a beneficial effect on ventricular remodeling. So, the study has examined the potential link between atrial remodeling and circulating high plasma levels of adiponectin in AF patients. In conclusion, the authors had reported the elevated plasma levels of adiponectin were linked to the presence of persistent AF with elevated serum carboxy-terminal telopeptide of collagen type I (CITP). So, measuring the adiponectin plasma levels would be useful for the assessment of AF [25].

In contrast, Choi et al. study in 2012 has analyzed the beneficial effects of adiponectin on cardiac function and reported the association with glucose metabolic, insulin resistance, and glucose metabolic. In obese individuals, serum levels of adiponectin were decreased as compared to the non-obese individual. The increased incidence of atrial fibrillation was linked to obesity. In conclusion, the paroxysmal AF was significantly linked to the lower plasma levels of adiponectin. The important risk of AF could be potentially hypoadiponectinemia [26].

Moreover, in 2018, Kim et al study have revealed the independent relationship between AF recurrence after catheter ablation for paroxysmal AF with elevated circulating levels of adiponectin in younger subjects than 65 years old individuals [27]. Besides, Macheret et al study examined the association between the high incidence of atrial fibrillation in an elderly population with elevated adiponectin concentration [28]. Similarly, according to the previous studies, it might be hypothesized that the link between AF and adiponectin might be age and gender-dependent. In addition, the pathogenetic aspects of atrial fibrillation were inflammation, atrial remodeling, and autonomic imbalance [29-31].

On the other hand, Ybarra et al. study revealed a novel inverse link between left atrial size with adiponectin which might inhibit atrial interstitial fibrosis as well as reverse atrial remodeling. More, adiponectin might be a connection between the heart and adipose tissue that influence cardiac remodeling [32].

2. Leptin

Leptin is a hormone that produces from adipose tissue and is secreted mainly from white adipose tissue, but also produced from non-adipose ones such as the immune system, placenta, mammary gland, and stomach [33,34]. Its regulation is achieved through numerous factors dependable on the metabolic status. The pathogenic mechanisms of leptin comprise obesity syndrome, metabolic dysfunctionalities, energy homeostasis, bone metabolic, and neuroendocrine function. The different mechanisms follow similar targets to cause the pathogenic pathways of leptin [33]. When leptin binds to its functional receptor and activates numerous transduction pathways, for instance, mitogen-activated protein kinase, Janus kinase JAK/ single transducers, activators of transcription, AMP-activated protein kinase, and phosphatidylinositol -4, 5- bisphosphate 3-kinase/ protein kinase B [35,36].

In addition, various studies have been confirmed that leptin levels correlate mainly with waist circumference and obesity. Under normal physiological conditions, leptin helps to reduce appetite, increase sympathetic activity, increase energy expenditure, improve insulin sensitivity and facilitate glucose utilization [37].

Obesity is an independent risk factor for the development of AF. So, obesity increase the prevalence of ischemic heart disease, hypertension, ventricular dysfunction, and congestive heart failure that might be contributed to the process of AF [38-40,10]. Similarly, Lin et al studies conduction in 2012 and 2013 have reported that Adipose tissues could yield many adipokines that have played electrophysiological effects through ionic profiles, contractility as well as changing action potential morphology [41,42].

Moreover, Fukui et al revealed that leptin signaling has been shown to contribute to angiotensin II- evoked AF and atrial fibrosis [43]. Likewise, Lin et al reported that Leptin regulates the Left Atrial electrophysiological features and calcium homeostasis. Leptin reduces the effect of isoproterenol-induced arrhythmogenesis- irregular rhythm or rate of heartbeat, which may play a favourable role in the pathophysiology of atrial arrhythmogenesis [42].

3. Leptin/Adiponectin Ratio

Adipocytes secrete from the two key hormones such as leptin and adiponectin. They both play several important physiological mechanisms. Their central role is in energy homeostasis and a marker of metabolic derangement [44]. Likewise, metabolic syndrome and obesity are categorized by elevated levels of leptin concentration in circulation which are corresponding to lower levels of adiponectin in blood. The leptin/adiponectin ratio is a marker of adipose tissue dysfunction. The leptin/ adiponectin ratio is associated negatively with Body Mass Index (BMI). It is powerfully connected with surrogate measures of insulin resistance (IR) such as homeostatic model assessment (HOMA) and the quantitative insulin sensitivity check index (QUICK) formulas for the measurement of insulin resistance. It is interrelated with insulin resistance better as compared to leptin and adiponectin values alone, even HOMA. The normal value of adiponectin/leptin ratio is equal or larger to 1.0 while the moderate -the medium risk is increased when its ratio is between 0.5 and 1.0, severe risk of cardiovascular diseases is indicated when the ratio is below 0.5 [45-47].

In addition, Finucane et al had reported that in non-diabetic adults, LAR is a useful marker of insulin resistance [48]. Furthermore, increased waist circumference increased vasoconstriction due to angiotensin II and decreased vascular response to acetylcholine were accompanying the imbalance of leptin/adiponectin. Both leptin and adiponectin have contradictory effects on subclinical inflammation and insulin resistance. Insulin resistance and type 2 diabetes mellitus are linked to proinflammatory cytokines such as interleukin-6 and TNF-α which are upregulated by leptin. In dissimilarity, adiponectin has anti-inflammatory properties and downregulates the expression and release of several pro-inflammatory immune mediators. Leptin/ adiponectin imbalance and angiotensin II are interrelated which are mediators of amplified risk of cardiovascular diseases and developing type 2 diabetes linked to abdominal obesity [49].

4. Tumoral necrosis factor-alpha

Tumoral necrosis factor-alpha is an inflammatory cytokine that is mostly formed by macrophages cells, also from another type of inflammatory cells. It is an acute inflammatory response protein that increased C- reactive proteins concentration and also regulates insulin resistance by interacting with insulin receptors [50]. Similarly, it played role in the regulation of lipid metabolism, adipokines synthesis as well as cholesterol metabolism [51].

Furthermore, Tumoral necrosis factor-alpha might be formed by inflammatory cells from the dysfunctional adipose tissue, like Interleukin-6. Numerous studies have shown that Tumoral necrosis factor-alpha is linked with all the components of metabolic syndrome that are involved in numerous metabolic syndrome pathways and alterations, in IR through a similar mechanism of Mammalian target of rapamycin (mTOR) and protein C kinase activation and systemic inflammation [52].

Moon et al study confirmed that tumor necrosis factor-alpha had a higher concentration in obese patients, even elevated levels in male subjects. Likewise, Body Mass Index, triglycerides, waist circumference, and diastolic blood pressure were positively correlated with tumor necrosis factor-alpha. But TNF-α was inversely correlated with HDL cholesterol but after adjustment for Body Mass Index and waist circumference, only the association with triglyceride levels persisted [53]. Similarly, Sookoian et al conducted a meta-analysis on 16 homogeneous studies that shown that systolic blood pressure, obesity, and serum insulin levels were positively correlated with tumor necrosis factor-alpha -308A gene variant and govern 23 per cent increased risk to develop the metabolic syndrome [54].

Moreover, TNF-α involvement has been shown in the pathogenesis of chronic Atrial Fibrillation. Valvular Atrial Fibrillation patients showed high levels of TNF-α, more severe leukocyte infiltration,

and more fibrosis. Higher TNF-α levels in the plasma and left atrial diameter in patients with rheumatic heart disease and chronic AF. Higher plasma interleukin-6 correlated with the presence and duration of AF and increased left atrial diameter [55].

Similarly, Saba et al. study explained the growing evidence that indicates the atrial electrical remodeling has been caused due to the tumor necrosis factor-alpha in which atrial myocytes isolated from failing heart overexpressing tumor necrosis factor-alpha, abnormalities in action potential propagation and Ca^{2+}handing which could contribute to the initiation and maintenance of re-entrant atrial arrhythmias including flutter and AF [56].

Ren et al. study had confirmed the comparison between control pulmonary vein (PV) cardiomyocytes, the tumor necrosis factor-alpha- treated pulmonary vein cardiomyocytes had a significantly larger amplitude of the delayed afterdepolarizations (DADs), larger transient inward currents, a smaller intracellular calcium transient, large diastolic intracellular calcium, a decreased sarcoplasmic reticulum ATPase (SERCA2a) expression, a longer decay portion of the calcium transient, larger $Na^{+} - Ca^{2+}$ exchanger currents, smaller I_{CaL} and a longer decay portion of the calcium transient. In conclusion, these findings had suggested that tumor necrosis factor-alpha could increase the PV arrhythmogenic activity and impair the calcium regulation, thereby causing inflammation-related AF [57].

In the same way, Deng et al. also demonstrated that tumor necrosis factor-alpha increased levels in the plasma as well as left atrial tissue which had a positive association with left atrial diameter in patients of chronic atrial fibrillation. It has resulted from rheumatic heart disease which collectively shown that tumor necrosis factor-alpha was strongly associated with atrial fibrosis in AF subjects [58]. Also, Tumor necrosis factor-alpha play's role in atrial remodeling including electrical, autonomic, structural, and contractile remodeling. It has been substrate for atrial fibrillation maintenance which has anti TNF- α therapeutic strategy for atrial fibrillation is theoretically appropriate [57].

Another study had concluded that tumor necrosis factor-alpha is involved in the pathogenesis of atrial fibrosis and changed connexin-40 expression in mice through the Transforming growth factor-beta / TGF-β signaling pathway increased secretion of Matrix metalloproteinases (MMPs) and activation of myofibroblasts. In summary, these changes might contribute to the arrhythmogenic substrate and processes of atrial fibrillation [59].

5. Interleukin-6

Interleukin-6 (IL-6) has played role in acute and chronic inflammation, the pathogenesis of the autoimmune disease, and immune cell development. It has increased the risk of developing diabetes mellitus that is linked with increased activity of the interleukin-6 gene [60]. Similarly, interleukin-6 is associated with all the components of the inner immunity and produced a pro-inflammatory effect. Despite that, various studies have been conducted to confirm that interleukin-6 also controls the process involved in the resolution of inflammation and also focuses on its anti-inflammatory function [61]. Various studies have been reported to confirm that interleukin-6 is associated with all five metabolic syndrome components but the main fact explains the dysfunctional adipose tissue has encourages macrophagic proliferation with an elevated level of interleukin- 6 production [62].

Likewise, Weiss et al. have investigated that interleukin-6 is linked with fasting plasma glucose, hypertension, and hypertriglyceridemia [63]. Similarly, Sarbijani et al. also gave the same result which has reported that elevated levels of interleukin-6 are related to metabolic syndrome severity [64].

Furthermore, the increased left atrial size was linked to the interleukin-6 because it is a well-known risk factor for atrial fibrillation. The authors have given the possibility in which interleukin-6 may result in atrial fibrillation because of left atrial remodeling [65]. In the same way, Psychari et al. study also shown the significant association between interleukin-6 with increased left atrial size which is an important risk factor for atrial fibrillation [66]. Additionally, postoperative atrial fibrillation has been linked to the polymorphisms in the promoter region of the interleukin-6 [67,68].

Besides, Gaudino et al. study had analyzed that the -174G/C lL-6 promoter gene variant could modulate the inflammatory response to surgery and also influence the development of postoperative AF. They suggested that inflammatory component of postoperative atrial arrhythmias as well as a genetic predisposition to this complication [67]. Similarly, Marcus et al. study has concluded that CAD subjects had increased levels of interleukin-6 and interleukin-6 -174 CC genotype that were significantly linked to AF. The authors did not find any association with other biomarkers such as CRP. In the end, the authors had suggested which interleukin- 6 is a uniquely important mediator in the pathophysiology of AF [69].

In the same line, Conway et al. study had concluded the existence of an inflammatory state such as elevated plasma interleukin-6, plasma viscosity, and CRP among the typical population with chronic atrial fibrillation. These indexes of inflammation are related to indexes of the prothrombic state which was also connected to the clinical variables including underlying vascular disease and co-morbidities rather than simply to the existence of atrial fibrillation itself [70].

Moreover, the Lazzerini study had given the suggestion systemic inflammation including elevated levels of interleukin-6 could rapidly induce atrial electrical remodeling by down-regulating cardiac connexins. These changes could significantly increase the risk for AF and related complications during active inflammatory processes [71].

6. Interleukin-10

Interleukin -10(IL-10) is a powerful anti-inflammatory cytokine that played role in the immune response to stop excessive activation and auto-damage, also in modulating insulin resistance and development of atherosclerotic [72]. Moreover, a cross-sectional study has been conducted on children and young adolescents, they have found that the plasmatic level of interleukin-10 was lower in obese or overweight children. Then, they concluded that interleukin-10 might be a marker of metabolic risk [73]. Interleukin-10 family members might induce numerous host defence processes against diverse infections, encourage innate immune response to alleviate infection-induced damage, sustain the integrity

Table 1: Summary of pathophysiological aspects of major Biomarkers of metabolic syndrome in AF

Biomarkers of MetS	Pathophysiological aspects in AF
Adiponectin	• Atrial remodeling • Elevated serum carboxy-terminal telopeptide of collagen type I (CITP) • The pathogenetic aspects of AF were inflammation, atrial remodeling, and autonomic imbalance • Influence cardiac remodeling.
Leptin	• Played electrophysiological effects through ionic profiles, contractility as well as changing action potential morphology • To contribute to Angiotensin II- evoked AF and atrial fibrosis • Reduces the effect of isoproterenol-induced arrhythmogenesis-irregular rhythm or rate of heartbeat • Play favourable role in the pathophysiology of atrial arrhythmogenesis
TNF-α	• More severe leukocyte infiltration, and more fibrosis • Increased Left atrial diameter • Atrial electrical remodeling • Abnormalities in action potential propagation and Ca2+ handling • Increase the PV arrhythmogenic activity and impair the calcium regulation • Associated with atrial fibrosis • Electrical, autonomic, structural, and contractile remodeling • Changed connexin-40 expression
IL-6	• Increased left atrial size • Rapidly induce atrial electrical remodeling by down-regulating cardiac connexins
IL-10	• Weakening the development of inflammatory atrial fibrosis
PTX-3	• The local production of the left atrium could reflect the local inflammation of atrial fibrillation
Ghrelin	• Atrial fibrosis due to atrial structural remodeling which resulted in repolarization by interfering with atrial excitement as well as pulse transfer, and differences in atrial conduction. • Cause changes in atrial ion channels which in turn could elevate the likelihood of repolarization and promote the onset of AF
Uric acid	• Left atrial and left ventricular remodeling • Causes atrial remodeling by oxidative stress, endothelial dysfunction, inducing inflammation, RASS activation • Causes electrical remodeling • Shortens the atrial refractory period • Establishes a reentry circuit in the atrium • Structural remodeling • Slows the velocity of conduction, thereby allowing reentry.
OxLDL	• Maximum diameter of the left atrium

and homeostasis of tissue epithelial layers.Moreover, even after viral or bacterial infections, these factors can accelerate the process of tissue healing [74].

In contrast, Esposito et al. reported that interleukin-10 levels were decreased in obese as compared with normal-weight women, but were lower in both groups that had metabolic syndrome criteria [75]. Similarly, Van Exel et al reported that reduced plasmatic levels of interleukin-10 in patients with metabolic syndrome and diabetes mellitus [76]. A recent study had conducted to explain the balance between inflammatory and anti-inflammatory including tumor necrosis factor-alpha and interleukin-10 which had been linked to atrial fibrillation recurrence after catheter ablation [77].

In contrast, Krishnamurthy et al. study had a conclusion which suggested that interleukin- 10 reduces the severity of proinflammatory responses and contributes to improving left ventricular function and remodeling with effects on Matrix metallopeptidase 9 (MMP-9) activation, fibrosis, and angiogenesis after Myocardial infarction which had happened due to the activation of signal transducer and activator of transcription 3 (STAT3) and suppression of p38 Mitogen-activated protein kinases (MAPKs) [78]. Additionally, Kondo study had examined that interleukin-10 plays a vital role in weakening the development of inflammatory atrial fibrosis and susceptibility to atrial fibrillation in mice with high-fat diet-induced obesity. In the obese human population, interleukin-10 could be a novel therapeutic way to stop atrial fibrillation [79].

7. Pentraxin -3 (PTX3)

Pentraxin-3 is a marker of local and general inflammation and immune response. Immune cells produced the PTX3 as a response to endotoxins, IL-1, bacterial substance and tumor necrosis factor-alpha. PTX3 has very low serum levels because it is an acute-phase protein. The levels of PTX3 rapidly raise as a response to diverse inflammation stimuli [80-82].

Recent studies have reported the association between increase PTX3 levels with the development and progression of metabolic syndrome. Likewise, Kardas et al study has reported that PTX3 levels were higher in subjects with obesity and metabolic syndrome. Moreover, they also have observed that increased PTX3 levels were linked with high triglycerides as well as low HDL cholesterol [83]. Similarly, Zanetti et al revealed that independent association between low HDL cholesterol level with PTX3 and in patients with metabolic syndrome and subclinical atherosclerosis had a higher level of PTX3 [84]. Further, a recent study found that after multivariate analysis, the severity of metabolic syndrome correlates with PTX3 which in turn correlation persisted for glucose level, HDL cholesterol and waist circumference [85]. As a result, PTX3 might be a valuable biomarker of metabolic syndrome prediction and needs further studies.

Moreover, Saeki et al study also demonstrated that PTX3 in the local production of the left atrium could reflect the local inflammation of AF. Additionally, PTX3 could be superior to other inflammatory markers that were reported to be elevated in AF [86].

8. Ghrelin

Ghrelin is secreted from the stomach and played role in appetite stimulation which is directly control by the hypothalamus by the activation of GH secretagogue receptor 1a as GHSR-1a. It is a neuroendocrine hormone and has the protective function of vasculature by antagonizing the effects of vasoconstrictors, for instance, endothelin-1, and promoting the effects of vasodilators, including nitric oxide (NO). with the help of hypothalamic AMP-activation protein kinase stimulation, it plays role in lipolysis. In contrast, many studies have shown there were two protective pathways (vasoprotective and lipolytic properties) of ghrelin that played role in protection against metabolic syndrome [87-89].

Moreover, Low levels of ghrelin are linked to the severity of the metabolic syndrome and associated with the different components of metabolic syndrome such as hypertension, insulin resistance, and obesity. When the number of metabolic syndromes derangements is increasing the levels of ghrelin also decrease [90-95].

Additionally, there are the following conditions that have explained the link between AF and ghrelin such as atrial fibrosis due to atrial structural remodeling which resulted in repolarization by interfering with atrial excitement as well as pulse transfer, and differences in atrial conduction. All events are occurred due to the presence and persistence

of AF. Atrial myocytes apoptosis was closely associated with atrial fibrillation [96].

However, studies have further reported that a decreased ghrelin level could cause changes in atrial ion channels which in turn could elevate the likelihood of repolarization and promote the onset of atrial fibrillation. Also, Dixit et al study has reported that inflammation has played a significant role in hypoxic, myocardial fibrosis, and ischemic conditions which triggered the AF that might additionally exaggerate inflammatory responses. So, ghrelin has strong anti-inflammatory effects and could inhibit the expression of interleukin- 6, TNF- α and interleukin-1β [97].

Therefore, ghrelin could be considered to be a possible anti-inflammatory compound. Sharma et al study also revealed that oxidative stress also played a role in the process of atrial fibrillation. So, ghrelin can inhibit oxidative stress [98]. In the same way, Ma et al study has shown that serum ghrelin concentration in patients with atrial fibrillation was reduced and significantly increased after treatment. Also, there was a positive association between the LVEF and serum ghrelin level in the patients of the atrial fibrillation group [99].

9. Uric acid

Uric acid is a heterocyclic organic compound with a molecular weight of 168 Dalton. $C_5H_4N_4O_3$ is the basic formula of uric acid. Metabolic breakdown of purine nucleotide gives uric acid which is the normal part of urine is excreted from kidneys and less amount is excreted from faeces. Furthermore, the most important organ of the body is the liver which produces uric acid. It can be produced from cells, tissues, and organs. The uric acid level is diverse and dominantly generated from endogenous purines and rests from the exogenous [100,101]. Moreover, Oxidative damage has occurred in the ischemic liver, diabetes, atherosclerosis, and chronic heart failure due to uric acid which is a circulating marker of it [102]. High levels of uric acid are an eminent risk factor for stroke, hypertension, dyslipidemia, and myocardial infarction. A positive association was found between uric acid and hypertension, BMI, triglycerides, and a negative association was found with HDL-C [103]. Also, a Greek patient first showed Atrial fibrillation associated with serum uric acid in the case-control study [104].

In addition, a high level of serum uric acid has a role in left atrial and left ventricular remodeling and finally in the development of atrial fibrillation. CRP, IL—6, and TNF are related to AF and left atrial enlargement. At the same time, they were associated with higher uric acid levels. Hyperuricemia and gout exert pro-oxidant effects and decrease nitric oxide bioavailability in the vessel wall, endothelial dysfunction, and inducing inflammation. All these effects promote the conduction changes directly and increase the incidence of cardiovascular risk factors for AF such as metabolic syndrome, diabetes mellitus, and hypertension. The linking pathophysiological issues between AF and serum uric acid were inflammation and tissue remodeling [105].

Further, increased levels of uric acid are related to permanent AF. Moreover, elevated levels of uric acid could be related to the burden of AF. Undoubtedly, more research will require to examine this potential association [104]. Similarly, Liu et al. study had demonstrated an independent link between AF and increased serum uric acid in hypertensive subjects. Further studies require to examine potential association and underlying pathophysiological mechanisms [106].

In addition, Zhang et al. study had reported the increased risk of AF was linked to hyperuricemia [107]. Similarly, Sun et al study revealed that in rural China, AF is positively linked to the SUA [108]. In the same way, Chen et al. study had demonstrated that s significant relationship between increased prevalence of AF and elevated SUA concentrations in the Chinese population. The authors explained the gender-specific mechanism underlying the association between atrial fibrillation serum uric acids levels. There was no exact underlying mechanism that has explained the association between uric acid and AF[109]. However, uric acid causes atrial remodeling by oxidative stress, endothelial dysfunction, inducing inflammation, RASS activation, which increases the risk of AF [110].

Similarly, uric acid causes electrical remodeling which further shortens the atrial refractory period and establishes a reentry circuit in the atrium [111]. Furthermore, Maharani et al study has reported that uric acid also causes structural remodeling and slows the velocity of conduction, thereby allowing reentry [110].

10. Oxidized Lipoprotein Lipase (OxLDL)

The product of lipid oxidation is the oxidized LDL as OxLDL and is also a marker of oxidative stress. The making of reactive oxygen species (ROS) is contributed by lipid oxidation and all the products form components of OxLDL. Lower concentrations of OxLDL, ROS and lipid oxidation products could be served as signaling components for pathways for cellular antioxidants. Cell damage and apoptosis were resulted due to the dysfunctional capacity of antioxidants in the cell and also seen in components of metabolic syndrome that contribute to the oxidation cascade [112].

Furthermore, Polovina et al. study (2017) has investigated the role of oxidative stress in the development of chronic kidney disease in AF. Further, the authors had concluded that AF had increased OxLDL as compared to sinus rhythm control [113]. Also, Tousoulis et al. study concluded a strong association between endothelial function and inflammation in patients with AF. The only independent predictor of OxLDL is the maximum diameter of the left atrium. The authors had given the suggestion that predicts oxidative stress status might be the left atrium distension [114].

Additionally, early afterdepolarization delayed afterdepolarization and intracellular Ca^{2+} levels were regulated by an increase of L type Ca^{2+} current and sarcoplasmic reticulum (SR) Ca^{2+} load. They were caused due to ox-LPL in human AF. Another study also reported the pathogenicity of human AF caused by ox-LPL due to endothelial dysfunction, enhanced I_{caL} due to LPC – induced mitochondrial ROS production in cardiac myocytes that resulted to increase native Ca^{2+} current (Ica) and vascular wall inflammation [115-117].

Conclusion

In conclusion, biomarkers of metabolic syndrome play a significant role in the development and progress of AF. Also, major biomarkers of metabolic syndrome such as adiponectin, Leptin, leptin/adiponectin ratio, TNF-α, IL-6, IL-10, PTX3, ghrelin, uric acid, and OxLDL,

played their pathophysiological role in AF.

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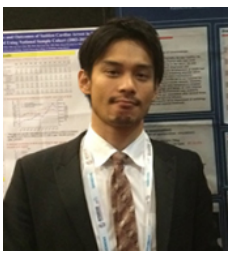

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